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Volume II (three numbers) is still available.

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BUSINESS MATTERS OF THE INTERNATIONAL ACADEMY

FROM THE OFFICE OF THE PRESIDENT

In accordance with the Bylaws of the International Academy Article I, Section 3, an

INTERNATIONAL MEETING ON EXFOLIATIVE CYTOLOGY

is scheduled for August 31 to September 2, 1961, immediately preceding the Third World Gynecology Congress. The place of the meeting will be Vienna, Austria.

Extracts from the Bylaws concerning the Scientific Session (*Article 1, Section 10*) : "... Papers presented at the Scientific Session shall be original papers which have never been presented or published. Material which has already been published or presented elsewhere may be considered in panel discussions. Fifty per cent of the Scientific Session shall be devoted to original papers, and fifty per cent of the time to panel discussions. ..."

For details concerning the International Meeting write to Dr. Ruth M. Graham, Roswell Park Memorial Institute, 666 Elm Street, Buffalo 3, New York, U.S.A. Suggestions for topics for panel discussions, and suggestions for topics of the main sessions are invited.

EDITORIAL

With the current issue of ACTA CYTOLOGICA, the journal also became the official periodical of the Brazilian Cytology Society (Sociedade Brasileira de Citologia) and the Mexican Association of Exfoliative Cytology (Asociacion Mexicana de Citologia Exfoliativa).

With the association of ACTA CYTOLOGICA with cytology societies other than the International Academy of Gynecological Cytology, the journal will undergo one change in policy. In addition to the present sections (such as the Symposia by Correspondence and Abstracts from the Cytological Literature), ACTA CYTOLOGICA will now publish REVIEW ARTICLES and ORIGINAL PUBLICATIONS on all phases of exfoliative cytology. These may be submitted to the editorial office by any author, without any special invitation.

Authors are invited to submit manuscripts on any phase of exfoliative cytology (respiratory tract, gastro-intestinal tract, reproductive tract, urinary tract, body fluids, experimental cytology, cytochemistry of exfoliated cells, cytometry of exfoliated cells, endocrinological cytology, technical problems in exfoliative cytology, etc.). The papers may be in English, French, German or Spanish.

The present pattern and style of ACTA CYTOLOGICA will be maintained. The current change in the editorial policy is merely in addition to the journal, in order to give our readers more information and to give the cytological author the opportunity to publish his papers in a periodical which is specialized in exfoliative cytology.

THE EDITORS

LETTERS TO THE EDITORS

CYTOLOGY OF THE IRRADIATED UTERINE CAVITY

TO THE EDITORS:

Reference is made to the paper of the above title by Emmerich von Haam, in the Symposium by Correspondence of Vol. II, No. 3, 1958 of ACTA CYTOLOGICA.

For the discussion of the cytology of the irradiated uterine cavity, two patients with adenocarcinoma of the endometrium have been followed by aspiration smears taken every second day after either radium application or the beginning of x-ray therapy. In addition, smears from the removed uteri have been studied. In our department patients with carcinoma of the body of the uterus have preoperative radiation as a rule with locally administered radium. If the uterus is not fitted for the radium "packing-method," preliminary x-ray is considered. Six weeks later a hysterectomy is done.

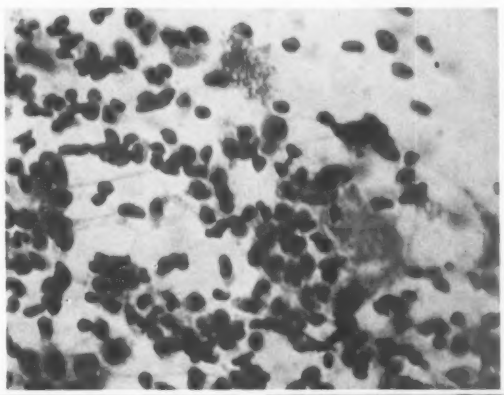

Fig. 1. Leukocytic and histiocytic exodus

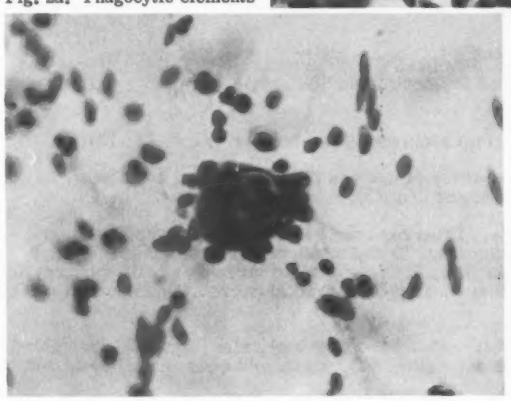

Fig. 2a. Phagocytic elements

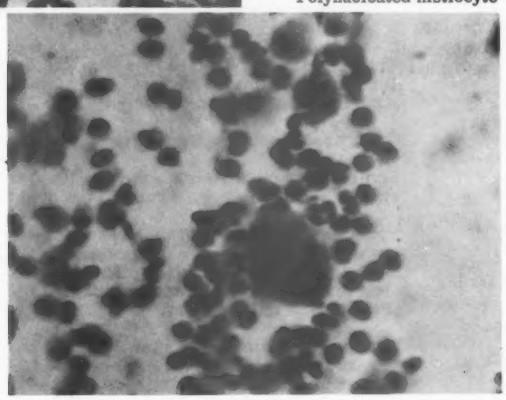

Fig. 2b. Polynucleated histiocyte

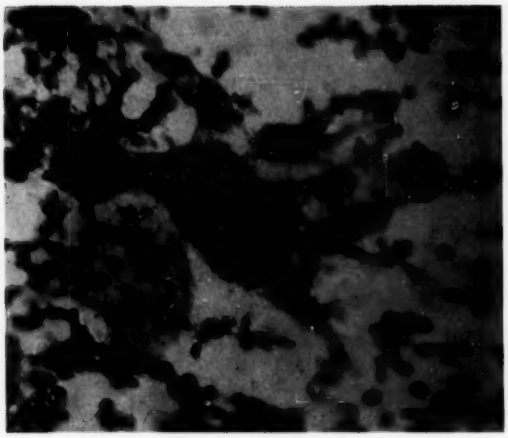

Fig. 3. Enlarged and swollen cells (probably endometrial)

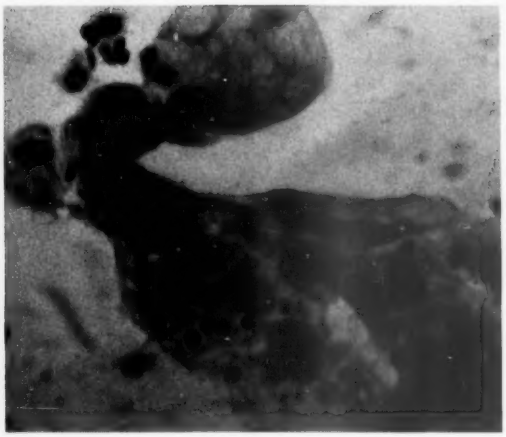

Fig. 4. Bizarre and distorted cells

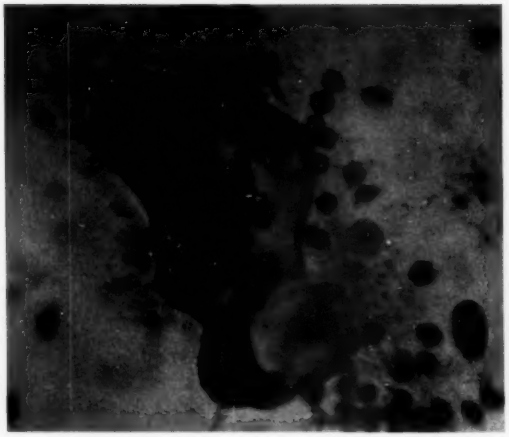

Fig. 5. Irregular vacuolization

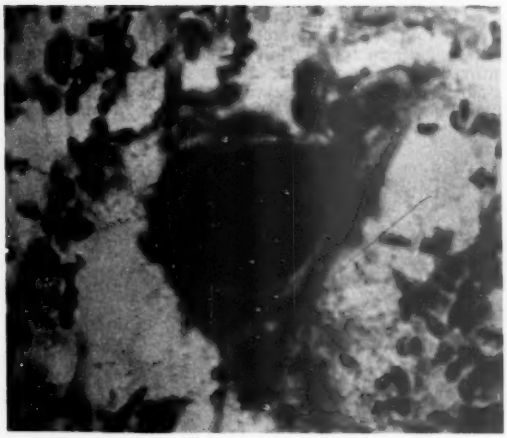

Fig. 6. Squamous cell metaplasia

Case No. 1:

The patient was 50 years of age. The dosage of radium was 3790 mgrhs (1890 in the uterus and 1890 in the vagina). Smears of day two showed leukocytic and histiocytic "exodus" as after menstruation, curettage or abortion (Fig. 1).

On day four, phagocytic elements and polynuclear giant-cells can be seen (Figs. 2a, 2b).

Beginning from day eight, irradiation changes of the tumor and the endometrial cells are visible. The cells are swollen, the nuclei enlarged (Fig. 3).

From day 18 to day 38 these changes increase. Bizarre, enlarged and distorted cells appear in the smears (Fig. 4). Irregular vacuolization (Fig. 5) and squamous cell metaplasia (Fig. 6) can be seen. Also, multinucleated giant-cells (Fig. 7) and so-called birds-eye cells (phagocytic elements) (Fig. 8) are easily found. In addition, nearly unchanged clusters of endometrial cells (Fig. 9) are still present.

The smears from the removed uterus showed irradiated endocervical cells (Fig. 10), irradiated endometrial cells (Fig. 11), irradiated tumor cells (Fig. 12), unchanged endometrial cells and multinucleated giant cells (Figs. 13, 14).

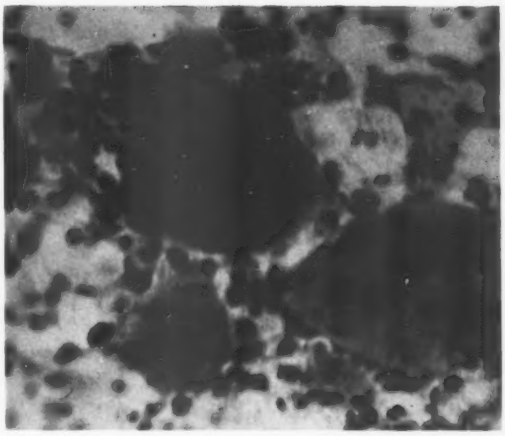

Fig. 7. Multinucleated giant-cells

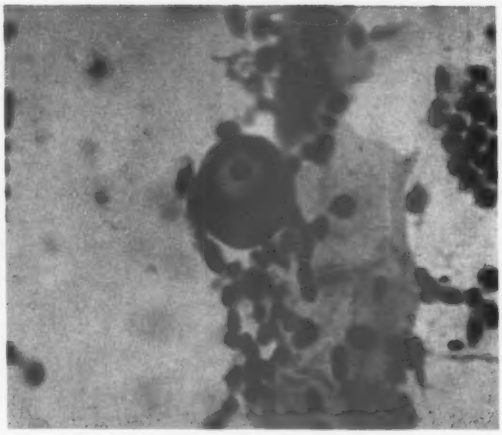

Fig. 8. Birds-eye cell

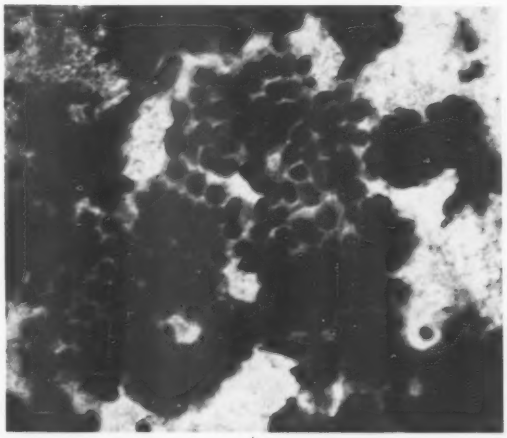

Fig. 9. Unchanged clusters of endometrial cells

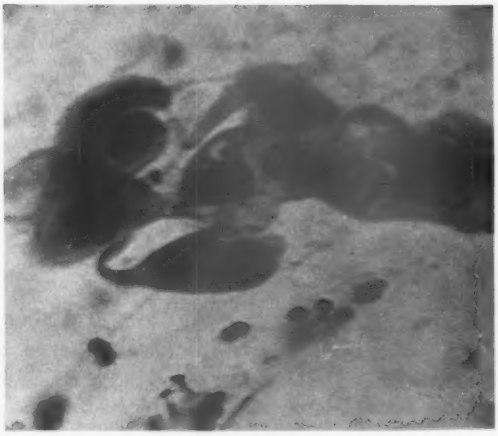

Fig. 10. Irradiated endocervical cells

Case No. 2:

The patient was 65 years of age. She had preliminary x-ray treatment (8500 r). In the aspiration smears only an increase in cellular debris and in leukocytic and histiocytic emigration could be seen.

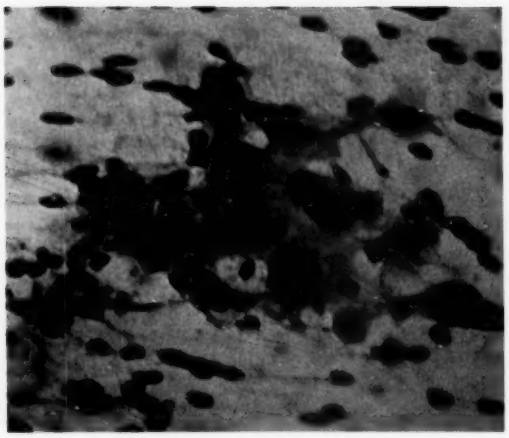

Fig. 11. Irradiated endometrial cells

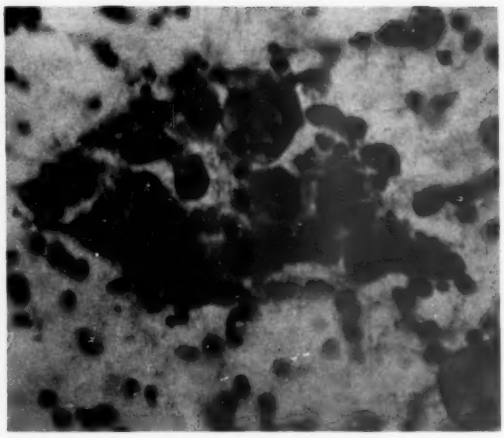

Fig. 12. Irradiated tumor cells

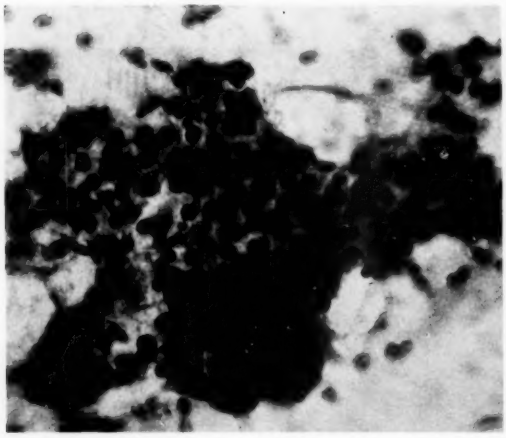

Fig. 13. Unchanged endometrial cells

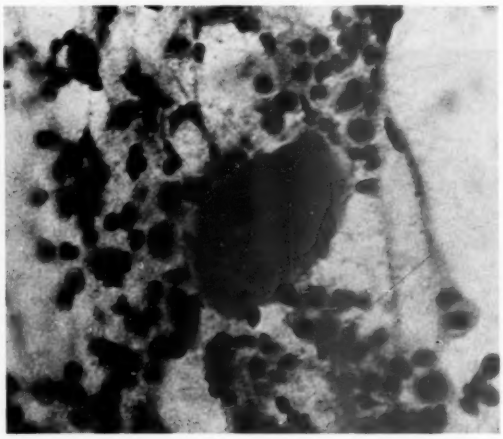

Fig. 14. Multinucleated giant-cells

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ABNORMAL NEUROLOGICAL HISTORY OF PATIENTS WITH EARLY CARCINOMA

To The Editors:

I found in my recent work that the appearance of gynecological cancer and cancer of other organs as well is regularly preceded by signs of slight, repeated, chronic encephalitis, probably of virus origin.

When we make a thorough study of the history of persons suffering from cancer or cytologically discovered pre-cancer, we find that either the patients or members of their families had (1) often and repeatedly suffered from virus infections and (2) had neurological or psychoneurotic symptoms which were in some cases obvious and in others obscure. They are as follows: severe headache, somnolence, insomnia without feeling of fatigue, nervous attacks sometimes epileptiform, unconsciousness, paresis, paresthesia, violent vomiting, disturbance of both sight and hearing, sciatica, trigeminal and intercostal neuralgia, fixed anxiety, inexplicable fear, melancholia, psychic depression and suicidal inclination.

These states sometimes occur after a psychic trauma. They are found in 80 - 90 per cent of the cases and, in general, belong to the rich symptomatology of encephalitis, which might be considered one of the main causes of malignant growths.

The causal connection between encephalitis and cancer could be explained by the repeated inflammatory conditions of important brain-centers (basal ganglia?) for the regulation of metabolism and for the differentiation of the peripheral tissues and organs. Cancer then develops in the region of the most active regenerative processes, e.g., in the squamo-columnar junction of the uterine cervix.

The recently increased number of malignant tumors (such as lung or breast cancer) is evidently in connection with the rise in the number of virus diseases. The introduction of pencillin and other anti-bacterial antibiotics into therapy disturbed the natural balance between bateria and viruses to the advantage of virus infections. The family disposition to malignant growths can be the result of the transmission of virus infections to members of the family due to long duration contacts with the patient.

I should appreciate very much if your readers could check up on my findings on their own patients and kindly let me know their personal opinions. To gain precise proof of this hypothesis is difficult, in my opinion, because the diagnosis of light encephalitis cases often escapes the neurologists. Investigations to find fine histological changes in basal ganglia of the brain in patients who died of cancer, could possibly be made more easily in well-equipped, special institutes.

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THE COLPOCYTOLOGIC INDEX IN THE HORMONAL EVALUATION OF THE VAGINAL SMEARS

To the Editors:

I was greatly interested to read, in Acta Cytologica, Vol. II, No. 1, 1958, the answers to Question 8 of "Hormonal Evaluation," and I wish to emphasize the advantages of using the colpocytologic formula and the Colpocytologic Index, which I proposed in 1949. This method has been usefully employed for ten years by many gynecologists for the evaluation of estrogen activity.

The colpocytologic formula results from the notation of one hundred cells of the vaginal epithelium exfoliated on the smear, and from the computation of the percentage of every cellular type (inner basal, outer basal, intermediate, karyopyknotic, granular, cornified cells). The main changes of the formula values follow the variations of the quantitative ratio between the deep layer elements (stratum germinativum or inner basal, outer basal, and intermediate cells) and the superficial layer elements (stratum corneum and granulosum or karyopyknotic, granular and cornified cells). Besides, it is well-known that the prevalence of superficial cells means a very high estrogenic activity, while the prevalence of deep layer cells characterizes the atrophic type of vaginal epithelium and a means a low estrogenic activity. On the basis of such knowledge I proposed a new method for an easier and quicker hormonal evaluation of the vaginal smear.

Therefore, I adopted a numerical index that comprises all the vaginal cytologic elements and registers truly and exactly all the changes, even the least, of the quantitative ratio between the deep layer cells and superficial layer cells. Consequently, I established the "Colpocytologic Index", that results from the following equation:

$$I = \frac{S \times 1}{P}$$

in which I is the Colpocytologic Index, S the amount of the karyopyknotic, granular and cornified cells, P the amount of inner basal, outer basal and intermediate cells, in the colpocytologic formula established on 100 cellular elements. Index values lower than 0.50 denote prevalence of the deep layer, and low estrogenic activity. Values higher than 1.00 denote predominance of the superficial layer, and marked estrogenic activity.

Numerous remarks show the usefulness of such a procedure. Gerli and Da Bormida pointed out that the Colpocytologic Index in the female newborn presents high values (from 1.60 to 1.90) on the first, second and third day, corresponding to the extensive desquamation of the vaginal epithelium. Then, on the following days, the Colpocytologic Index decreases rapidly, so that within the fourth to the fifth day the "inversion" of the Colpocytologic Index occurs, which abruptly decreases to 0.21 (middle value). This corresponds perfectly to the changes that occur during this period in the vaginal mucosa of the newborn, in which, after the fall in placentar hormones, the epithelium remarkably diminishes in thickness, due to desquamation of the superficial layer. If, at the same time, we determine the Eosinophilic Index, we find irregular variations, with an increase during the first and second day, a decrease during the fourth day and a new increase on the seventh day. Therefore, if we consider the Eosinophilic Index only, we cannot obtain a satisfactory hormonal evaluation; this has been proved by Gerli. The changes of the Colpocytologic Index are parallel to those of the urinary level of

the total estrogen substances. Caminiti observed that the injection of one mg of stilbestrol in women who previously had undergone bilateral ovariectomy, resulted in an evident increase of Colpocytologic Index on the first day after the injection to values higher than 1 (1.17-1.56) and at the same time the total estrogenic substances increased in the urine from γ 0-50 to γ 60-200. On the third and fourth day after the injection the Colpocytologic Index and the urinary estrogen level diminish similarly. The Eosinophilic Index, studied at the same time, did not show consistent values and revealed various curves. Consequently it is evident that the Colpocytologic Index is more significant than the Eosinophilic Index in evaluating the estrogenic activity. On the other hand, we must also consider the pseudo-eosinophilic picture resulting from overstaining and from vaginal irritation or infection. It must be realized also that cervical mucus, with which the exfoliated cells come into contact, can produce pseudo-eosinophilic pictures. This has been shown again more recently by Gerli.

In the normal woman, as stated by Randazzo, the injection of 3 mg of stilbestrol between the ninth and eighteenth day of the menstrual cycle results in an evident increase in the Colpocytologic Index, which reaches its peak after 24-48 hours and then gradually diminishes to the initial values after three days. The degree of increase varies in different women and this denotes the different individual receptivity. The increase is more prominent in subjects in whom the initial value of the Colpocytologic Index is higher.

Employing the same method of the colpocytologic formula and Colpocytologic Index determination, significant observations have been made by Anzisi in normal pregnant women and in toxemias of pregnancy; by Berlingieri and Labate in threatened abortion, in missed abortion and in the post-abortum; by Frontera in puerperal women and in the lactation period; by Milani and Padovani in menopausal women after treatment with Filatov's method; by Gerli in cases of uterine myoma after treatment with estradiol benzoate; by Gerli and Sora in myofibromatous women submitted to short-wave stimulation of the diencephalon and pituitary; and by Mutti in women previously submitted to intrauterine radium treatment. Gerli and Berlingieri also studied the comparative behavior of the Colpocytologic and Karyopyknotic Indices and pointed out that the Karyopyknotic Index, although it does not show curves identical to those of the Colpocytologic Index, nevertheless, presents similar changes. In the determination of the colpocytologic formula is implied the notation of the karyopyknotic cells. Therefore, the colpocytologic formula and Colpocytologic Index give a more complete and faithful picture of changes in the vaginal epithelium. For this reason we recommend our own procedure for rational hormonal evaluation of the vaginal smear.

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ACTA CYTOLOGICA · 1959

Vol. III REVIEW ARTICLE No. 1

A Critical Review of Gastric Cytology

R. O. K. SCHADE, M.D., L.R.C.P., M.R.C.S.

On the 29th of January, 1881, Billroth performed the first partial gastrectomy for gastric carcinoma. This operation was the beginning of a new era in surgery and raised hopes that a cure for gastric carcinoma was at hand. However, the rapid technical advances in gastric surgery were not matched by any significant improvement in long term results. Gastric carcinoma has remained an important killing disease in most countries.

It is not surprising to find that even at the close of the nineteenth century, a growing body of opinion believed that a permanent cure from gastric cancer could be achieved only if diagnosis was possible to permit intervention at the earliest stages of neoplasia.

To this end Rosenbach (32), Reineboth (29) and others attempted the examination of gastric aspirates and succeeded occasionally in making a histological diagnosis of carcinoma on desquamated fragments. In 1909, Marini (18), working in Bologna, published an outstanding contribution on the problem of cytological diagnosis. His technique for obtaining material and his diagnostic criteria for the malignant cell are essentially those we use today. His equipment for diagnosis, simple as it was, must have made his achievements difficult to obtain. He was convinced that cytology alone could establish a diagnosis of carcinoma long before physical signs made the diagnosis obvious, when treatment may already be of little avail and may give only temporary relief.

With the development of radiological and gastroscopical techniques as well as with the introduction of new laboratory tests, the early work on gastric cytology has been forgotten. Papanicolaou and his co-workers stimulated new research into the possibilities of diagnostic cytology, first in the field of gynaecological cytology and subsequently by applying cytological diagnosis to other organ systems.

For the study of gastric cytology it is of the greatest importance to realise that the mucosa from which the carcinoma arises is of far greater complexity than, for example, the mucosa of the cervix or the bronchial tree. Deep in the gastric

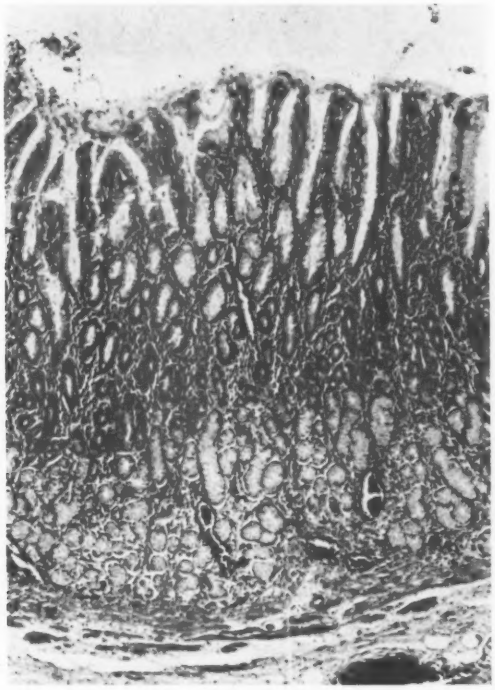


Fig. 1

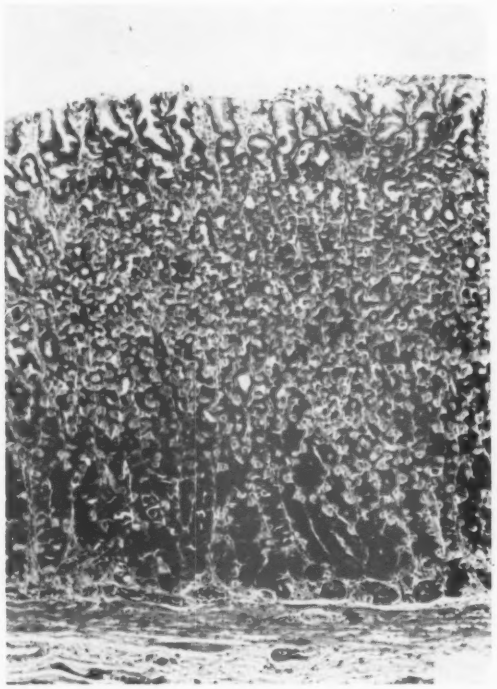


Fig. 2

From the Department of Pathology, King's College Medical School, Durham University, Newcastle upon Tyne 1, England, U.K.

lining epithelium which produces the gastric mucus, a mucoprotein, lie the specific structures of antral or corporeal mucosa. Although it is true to say that the bulk of the exfoliated layers which the cytologist examines is surface epithelium, it is essential for diagnostic accuracy that he be familiar with all other cellular components of the gastric mucosa in health and disease. The presence of these multiple histological components within a normal mucosa results in a very varied cytological picture. If one adds to the normal cells those that show morphological changes as the result of inflammation or neoplasia then the cellular picture becomes very complex.

Therefore, it is postulated that successful gastric cytology can be performed only if the cytologist is prepared to study and compare, whenever the opportunity arises, the cytological picture with the histological appearances of the gastric mucosa.

The histological study of numerous gastric specimens leads us to understand the process of exfoliation. From the mucosa of the antrum and body of the normal stomach few cells are exfoliated (Figs. 1 and 2). Indeed, the mucus covering the mucosa is practically acellular. This corresponds with the examination of lavage specimens of normal subjects in whom generally only an occasional mucosal cell can be found and no inflammatory cells whatsoever. It appears likely that some of the cells will disintegrate as the result of the acid levels within the normal stomach. In contrast, exfoliation in cases of acute gastritis, and particularly in chronic gastritis, is often very marked. Consequently, gastric lavage specimens of such cases show a profusion of mucosal cells—both single and in sheets —accompanied by masses of inflammatory cells such as polymorphs and plasma cells. Sections of cases of acute and chronic gastritis give a clear indication as to the mechanism of exfoliation. Figs. 3–8 show the superficial portion of gastric mucosa in a case of gastritis. The covering epithelium is pushed away from the underlying stroma which is packed with inflammatory cells. In the epithelial cells transmigrating polymorphs can be seen, a picture which is familiar to all cytologists. Once the epithelium is exfoliated, a so-called 'Leistenspitzenerosion" has developed, from which numbers of inflammatory cells pour into the gastric cavity. It is obvious that by the same process abnormal epithelia can be exfoliated, such as the epithelium of intestinal metaplasia. In cases of surface carcinoma the exfoliative process is often more marked than in all other previous mentioned conditions (Figs. 9 and 10). These observations on histological preparations have led us to the important conclusion that the exfoliative process should not be interfered with by the method chosen for the collection of gastric cellular material, as we shall see later.

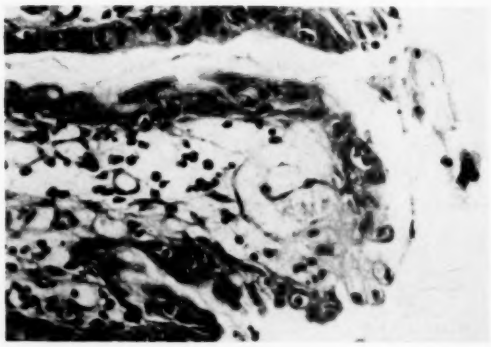
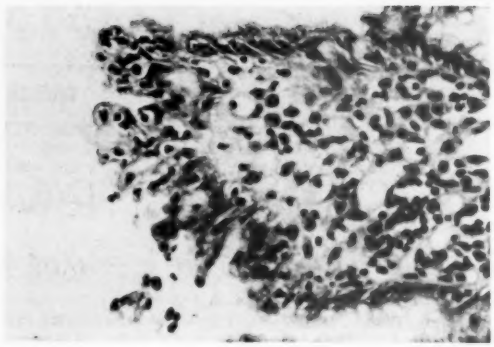


Fig. 3

The next important point is to define the aims of gastric cytology. A survey of the literature gives the impression that the purpose of cytology is directed to a high percentage accuracy and not to early diagnosis. Diagnostic accuracy is highly desirable but does not in itself prove that cytology is a more efficient weapon for cancer diagnosis than radiology or gastroscopy. It must be the cytologist's aim to diagnose the equivalent of a cervical carcinoma in situ, namely the gastric surface carcinoma (Fig. 11) which, as we believe, is generally superimposed on a chronic atrophic-hypertrophic gastritis and which forms the initial stage of the carcinomatous tumour. If there is a relationship between chronic gastritis and carcinoma, the cytological picture of the first named condition must be clearly defined. By so doing we can follow up the patient with chronic gastritis and probably detect developing carcinoma before deep invasive or even metastatic growth has occurred. As yet, very few of the large number of publications



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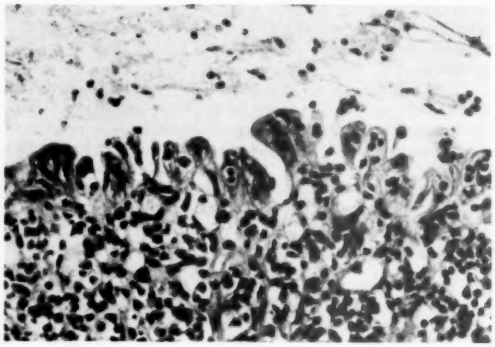

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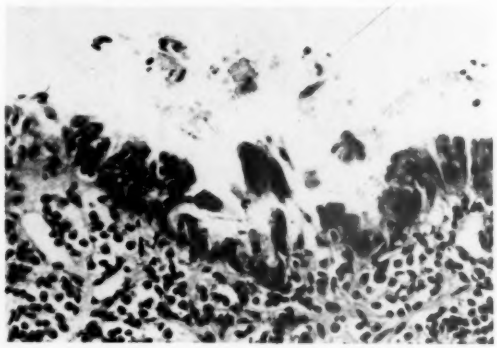

Fig. 6

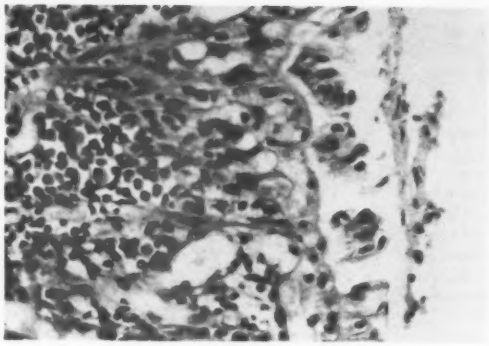

Fig. 7

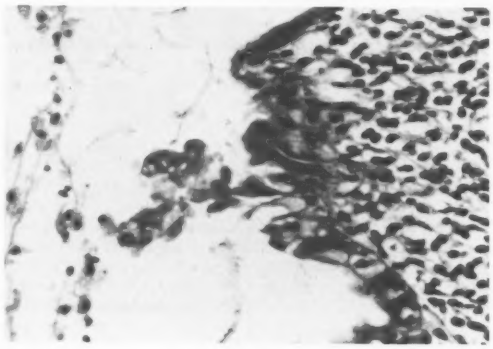

Fig. 8

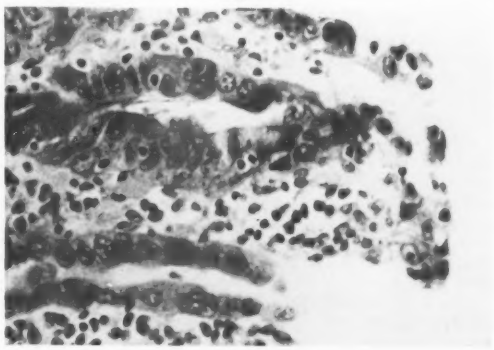

Fig. 9

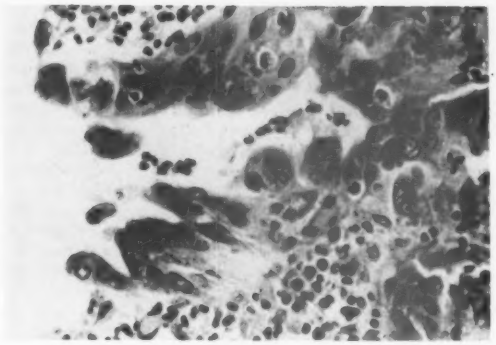

Fig. 10

Fig. 11

on gastric cytology have described surface carcinomata diagnosed by cytology.

The surface carcinoma of the stomach has been recognised as an entity long before the beginnings of gastric cytology. A comprehensive review of such cases can be found in the publications by Konjetzny (16), Prinz (25) and others.

We have now to discuss the methods for collection of suitable cellular material. Already, three main types of methods can be recognised: firstly the techniques that rely on mechanical removal of cells, secondly those that utilise mucolytic agents and thirdly those that consist of simple gastric lavage either with saline, Ringer's solution or a buffered type of solution.

Before describing these methods in detail, I would like to stress that it is most desirable that one or more trained technicians in any institution should be made responsible for the preparation of the patient and the subsequent collection of material. If cytological material is collected in this way the material is comparable and representative of the pathological processes within the gastric cavity. If, on the contrary, the collection of material is left to a variety of staff—nurses, students, housemen, etc., far more rigid standards have to be applied when dealing with the material. More often than not, multiple tests will have to be performed to overcome the deficiencies of the material before arriving at an accurate diagnosis.

Henning's "Zelltupfsonde" was one of the first instruments devised and relies on the mechanical removal of cells (11). This instrument possesses at its operative end a detachable foam rubber sponge which can enter the stomach within the cover of a rubber tube, thereby avoiding contamination by oral or oesophageal mucosa. The sponge is brought into contact with the gastric mucosa by pushing it beyond the distal end of the rubber tube and moving it either blindly or under x-ray guidance over the gastric mucosa to be examined. Before withdrawing the entire instrument, the sponge is pulled into the tube. Finally, the sponge is washed in saline. After centrifuging, the saline cellular deposit is examined in the usual fashion. The inherent weakness of this instrument consists in its inability to obtain cell samples from the entire gastric mucosa, and its virtue lies in obtaining uncontaminated gastric cellular material. It is an instrument most useful for the study of diffuse inflammatory lesions of the stomach.

Papanicolaou, Cooper and Panico described the gastric balloon. This instrument depends on the abrasive action of a knotted net coverin ga ⅜balloon which is introduced deflated. One depends on the peristaltic action of the stomach for the propulsion of the balloon from the cardiac end to the pylorus.

The cellular material is obtained by rinsing the balloon and net. The rinsing fluid is centrifuged and the sediment examined. The instrument is cumbersome and unpleasant in use for the patient although it cannot be denied that good cellular material can be obtained. It is doubtful, however, whether the most distal part of the pyloric antrum can easily be reached by this method. Panico's antrum balloon is an attempt to overcome the difficulties inherent in the abrasive balloon. The last mechanical method is Ayre's gastric brush (1), an instrument which, by means of a rotatable bi-winged brush, removes mechanically cells from the mucosal surface. As with all tubes with a relatively narrow diameter passing into the stomach, there is very little control over the position of the brush in the stomach and, in consequence, no indication from which area of gastric mucosa the cellular material is derived.

There can be no doubt that the mechanical methods are in the first instance too unpleasant for the patient, too cumbersome to use and the results achieved do not reflect the pathological processes in progress from pylorus to cardia. Furthermore, patients are unwilling to undergo repeated tests because the passing of these instruments, even in skilled hands, causes them a certain amount of discomfort; and it is often advisable, sometimes essential, to perform several cytological tests to reach a conclusive diagnosis.

Lavage methods using mucolytic agents can be divided into two groups, those that use papain as mucolytic agent and those that use α-chymotrypsin. The first named method was developed by Rosenthal and Traut (33), the second by Rubin and Benditt (37).

Papain solution is not consistent in its action and varies in effectiveness from patient to patient, while α-chymotrypsin is more reliable in its action. We have tried both methods and have derived no benefit from the use of either agent. On the contrary, we found that α-chymotrypsin dissolves the mucus derived from the bronchial tree, and by doing so alveolar phagocytes and other respiratory epithelia become scattered throughout the smears adding, in some instances, to difficulties of interpretation. We have used α-chymotrypsin for large numbers of pernicious anaemia patients in whom routine lavage is erformed to detect any development of cancer in its initial phases. Pernicious anaemia cases, particularly when complete gastric atrophy has developed, generally contain few gastric cells in ordinary lavage specimens. The addition of α-chymotrypsin has made no difference to the cellularity of the smears.

We have, therefore, little doubt that the simple lavage method as advocated in 1948 by Graham, Ulfelder and Green (8) is by far the easiest method for collection of material. It does not matter whether the lavage fluid consists of saline, Ringer's solution or a buffered solution. The most important features of this method are, firstly, a forceful injection of the lavage fluid into the stomach, followed by multiple aspirations of some of the fluid and repeated forced reinjection. Furthermore, the greatest care should be taken to vary the patient's position so that all the gastric mucosa is washed by the fluid in turn. If these precautions are taken, then adequate material is generally obtained. In many of our cases we perform two or three gastric lavages routinely and thereby reduce the risk of missing malignant change to a minimum. We leave it entirely to the patient whether the Levene tube, used for the test, is introduced via the nasal passages or the mouth. By doing so, the patient is usually cooperative and consents to multiple tests if required. It is the job of the cytologist to be able to differentiate the varying cell types.

The preparation of the patient is of considerable importance for a successful lavage. Generally, we ask the patient to fast from 6 o'clock at night until the test has been performed, although fluids may be taken. A lavage, before the actual test lavage is performed, a procedure suggested in some papers, is entirely undesirable for several reasons.

Firstly, the cell content of the subsequent lavage fluid may be very low. Secondly, the gastric flora and small residual particles of undigested food are removed. Changes in the gstric flora provide part of the evidence of pathological processes in the stomach. From this evidence, it can be judged whether the stomach is achlorhydric or not and whether there is obstruction or a patent pylorus.

After centrifugation the supernatant fluid is decanted and the sediment spread out on four to six slides. The spreading is again of considerable importance. We use stiff chrome-nickel wire loops to position the sediment with parallel strokes in thick layers on the slide. By doing this one gets a large amount of material on the slide, and thick and thin fields alternate with each other. The material is fixed in the usual fashion and stained after Papanicolaou's method which gives, even in the thick smears, a clear picture. The scanning is performed by several people. The report comments on the presence of a normal or abnormal flora, the type of inflammatory cell present, the epithelial cells seen and the presence or absence of food particles. A final diagnostic impression is given.

The most common inflammatory cell seen in the gastric washings is the neutrophil polymorph. Its appearance is altered in the smears from patients with normal or high acid levels but remains well preservedin the achlorhydric stomach. It is present in large numbers in cases of acute gastritis, acute and chronic ulceration and surface carcinomata. Eosinophil leukocytes have only rarely been observed. The lymphocytes are, from a diagnostic point of view, not of great importance, apart from those rare cases of gastric lymphoma, reticulum-cell-sarcoma, etc. On the other hand, plasma cells are very frequently encountered. Their appearance in the Papanicolaou stained film is characteristic. The cytoplasm stains from greenish to brownish red, and the nucleus has the typical cartwheel appearance. These cells are commonly encountered in cases of chronic atrophic gastritis, and in cases of chronic atrophic gastritis associated with surface carcinoma so that they are of considerable cytodiagnostic importance. Erythrocytes, when originating from the gastric mucosa, are generally well mixed with the other cellular components and appear diffusely scattered within the smears.

Turning to the epithelial cells from the gastric mucosa, these show a considerable variation in appearance. One rarely finds the high tall columnar epithelium which forms the lining of the normal stomach. This is not surprising as the greater number of patients presenting themselves for gastric lavage are complaining of gastric afflictions. The epithelium seen with greatest frequency is a modified type common to all cases of diffuse inflammatory lesions in the stomach. The epithelium appears shorter and plumper, while the nucleus commonly is situated centrally. Although the nuclear membrane in the tall epithelial cell of the normal mucosa does not stain distinctly, that of the nucleus in cases of gastritis appears sharply stained though not generally thickened. The nucleus may contain several, but small nucleoli. If these cells present themselves in clusters, then the cell boundaries are generally distinct and the epithelial cells show a regular, orderly arrangement (Fig. 12, 13). The features described leave no doubt of their nature or origin. With progressive gastritic changes it is observed that the epithelium presents changes which are generally referred to as intestinal metaplasia (Fig. 14). It is natural that these cells also desquamate. In our opinion, their variation in appearance represents the greatest problem to the cytologist. They are of round shape, larger than the ordinary gastritic surface epithelia and contain one large or multiple small mucous globules. The nucleus is commonly pushed to one side and often flattened, producing the typical signet-ring appearance. Often they contain one single or a number of polymorphs (Fig. 15). With the help of special staining methods—I refer to those that stain specifically acid mucopolysaccharides—it can be shown that these cells contain mucus which is of a different nature to that of the normal or even the gastritic surface epithelium. In some cases their variation in size makes it impossible to differentiate them from tumor cells derived from a mucoid carcinoma (Fig. 16).

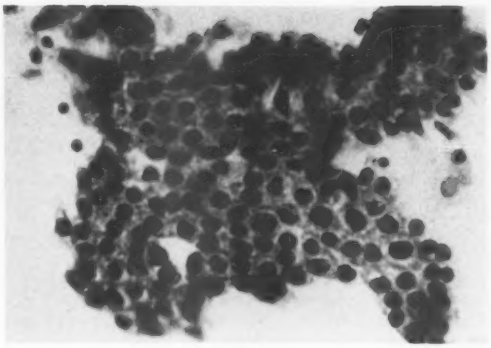

Fig. 12

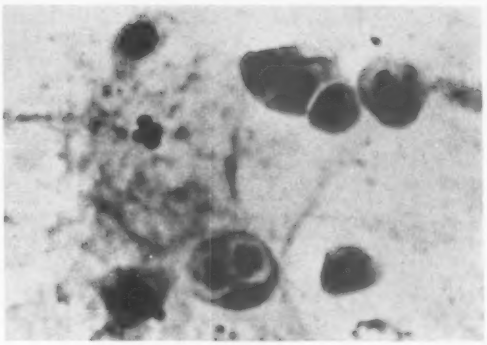

Fig. 15

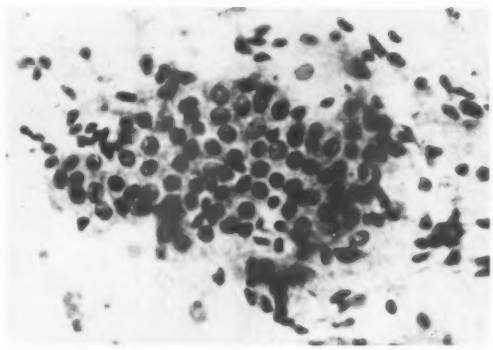

Fig. 13

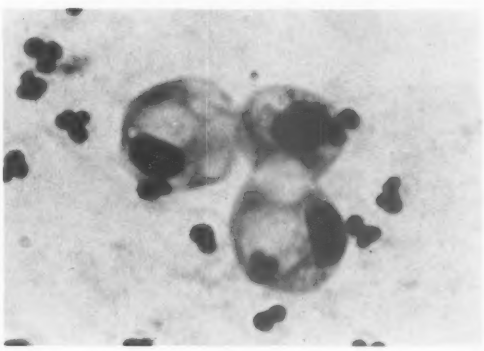

Fig. 16

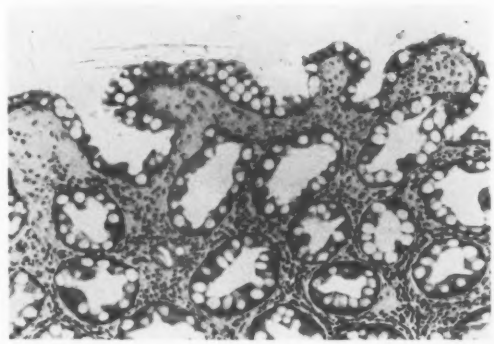

Fig. 14

Some authors have described specific cells occurring in pernicious anaemia which are considered by them to be typical of that disease. Our own studies do not confirm this opinion. The histological lesion of pernicious anaemia varies considerably. According to our findings and contrary to other opinions, it affects the pyloric antrum and the fundus. The lesion seen differs in no way from a chronic progressing atrophic gastritis with intestinal metaplasia and the cellular picture corresponds, therefore, to the varying stages seen in the course of this disease. A recent case of pernicious anaemia of 16 years duration, in which, finally, a carcinmoa developed showed in pyloric antrum and the resected fundal portion of the stomach chronic atrophic gastritis with widespread intestinilisation.

Turning to the malignant cells, I would like to stress that far too many attempts have been made to arrive at a histological diagnosis on cytological grounds. It is quite impossible when dealing with gastric cytological specimens to predict the tumour type. In addition, it is futile to aim at such by diagnostic refinements. It is obvious from a study of the histology of gastric carcinoma that these tumours rarely have a uniform structure throughout. For example, it can regularly be noted, provided sufficient material is examined, that one part of a tumour is adenocarcinomatous while in a neighbouring area it is composed of solid epithelial strands or tissue resembling mucoid carcinoma. I believe that it is even unwise to speculate on cytological grounds whether the cells are part of a differentiated or dedifferentiated tumour. The following photographs illustrate this point. Fig. 17 shows a group of cells which, from the cytological point of view, were clearly of a malignant nature and apparently well differentiated. They were most likely from an adenocarcinoma and yet the histological appearance of the tumour showed adeno and mucoid carcinoma in equal proportions.

The malignant cells present themselves in an extraordinary variety of form and shape. Fig. 18 shows a group of cells with only faint outlines of the cytoplasm. Within the group there is considerable variation in nuclear size. The nuclear membrane is distinct but not prominent. The cells lie in a background of lysed blood. Numerous groups of similar features were seen in this case which proved to be an anaplastic carcinoma. Fig. 19 consists of six malignant cells with well preserved cytoplasm, considerable variation in cell size and a marked shift of the nucleo-cytoplasmic ratio in favour of the nucleus. The nuclei stained very densely and were very hyperchromatic. Fig. 20 illustrates an easily diagnosable syncytium-like group of malignant cells. The cells again show the altered nucleo-

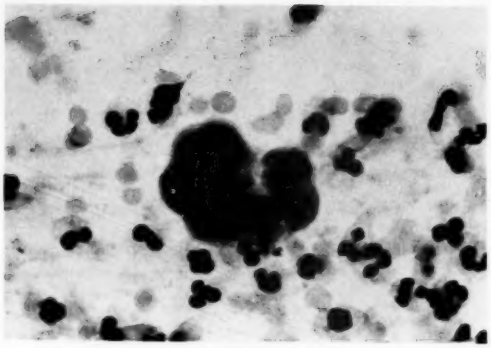

Fig. 17

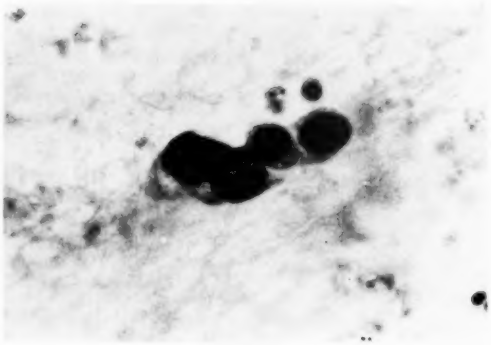

Fig. 18

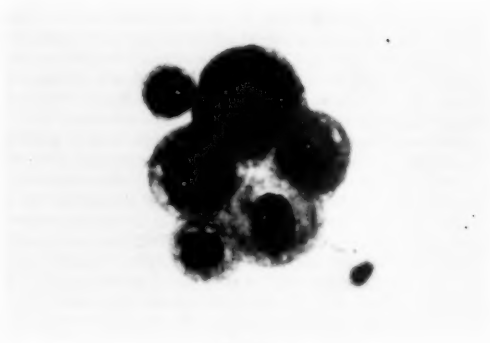

Fig. 19

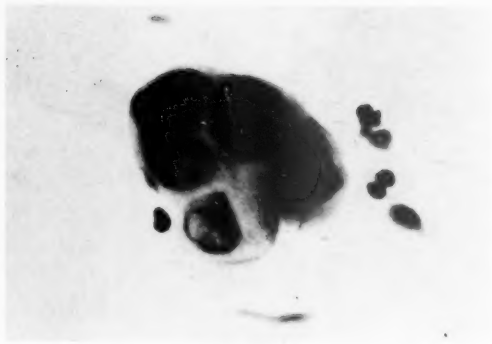

Fig. 20

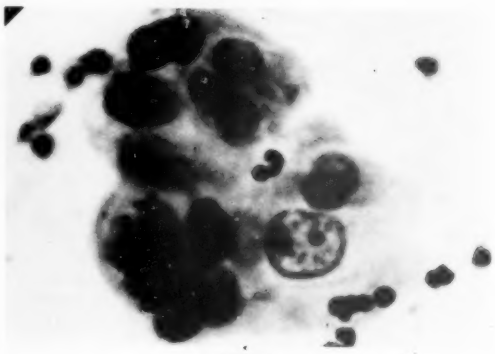

Fig. 21

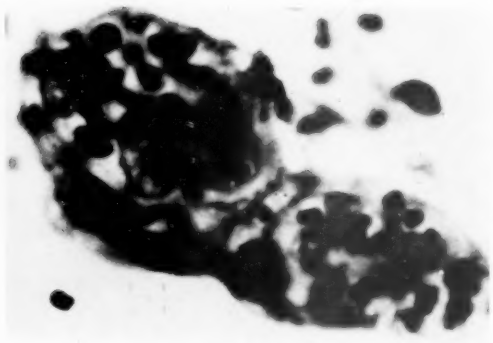

Fig. 22

cytoplasmic ratio. The nuclei are partly hyperchromatic with distinctly staining nuclear membrane. The nucleoli are enlarged. Fig. 21 shows once more a syncytium-like arrangement of malignant cells with complete loss of cell boundaries and considerable overlapping of nuclei, a characteristic feature of clumps of malignant cells. One of the cells present shows a giant nucleus with a very distinct, thickened nuclear membrane and enlarged nucleoli. Fig. 22 shows malignant cells with numerous polymorphs in their cytoplasm which have probably been actively phagocytosed by the malignant cells. Fig. 23 shows a large clump of malignant cells. The features of note are one cell in mitosis—an uncommon occurance—and a second cell with a large amount of cytoplasm which is filled by a huge mucous droplet. In spite of the mucus-laden cells demonstrated, the neoplasm, when sectioned, showed largely the appearances of an adenocarcinoma of good differentiation. Giant tumour cells (Fig. 24, 25) are not very commonly met with. Those shown were exfoliated from a slightly dedifferentiated adenocarcinoma.

Large sheets of malignant cells (Fig. 26) are not seen frequently in simple lavage specimens but when present they leave no doubt about the diagnosis. We have found that the cells are present in larger numbers and occur as large formations more commonly in small actively growing tumours than in cases of large ulcerated neoplasms. We share this experience with the Chicago group of cytologists. The appearances of the malignant cells undergo considerable changes in the obstructed stomach. Commonly, they lose their cytoplasm

and appear as naked nuclei. Cytological specimens from such cases (Fig. 27, 28) do not give rise to faulty diagnoses, as the nuclei remain apparently preserved for some considerable time before they lose their distinctive features. Very often the tumour cells seem to stick to formed food fragments (Fig. 29). The more marked the obstruction the less likely is one to find malignant cells as they fall victim to the fermentative processes in the stagnating gastric contents.

The wide variety of appearances of gastric malignant cells demands, if accurate diagnosis is to be achieved, considerable experience and constant comparative histological studies.

If one is willing to accept these stipulations, then gastric cytology proves itself more reliable than the conventional diagnostic methods.

In a series of 522 consecutive cases which had cytological investigations on one or several occasions previous to operation, an overall accuracy of 96.4% was achieved. The cases consisted of nearly equal proportions of carcinoma and ulcer cases. The accuracy within the cancer group was higher (97.6%) than that in the ulcer group (94.8%). The number of false positive results in the ulcer group was higher than that of the false negative results in the cancer group. This is no doubt due to the changes in the epithelial cells produced by inflammation and regenerating. Regenerating cells may exhibit variations of cell size, nucleus and nucleolus which are distinguishable only with difficulty from those seen in carcinoma. This fact explains largely the objections raised by conservative morbid anatomists against cytology as an accurate means of diagnosis.

The figures of greatest importance, however, are not those quoted so far but the fact that 10.5% of all cancer cases (258) remained undiagnosed by radiology and that 6.2% were, on clinical and radiological grounds, not suspect of carcinoma. They were diagnosed cytologically as the result of a general investigation of patients with vague clinical complaints. The operative specimen showed on naked eye and histological examination the appearance of surface carcinomata, a type of tumour which, after radical operation, should give the patient a chance of a complete cure. The examination of surface carcinomata has made us aware that they are always accompanied by severe atrophic gastritis, often with widespread intestinal metaplasia. There is a close relationship, possibly of aetiological significance, between chronic atrophic gastritis and the development of carcinoma. If this is the case, re-

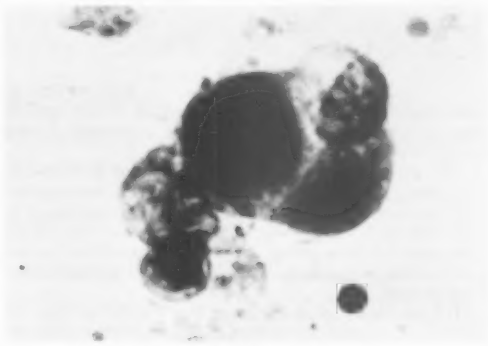

Fig. 25

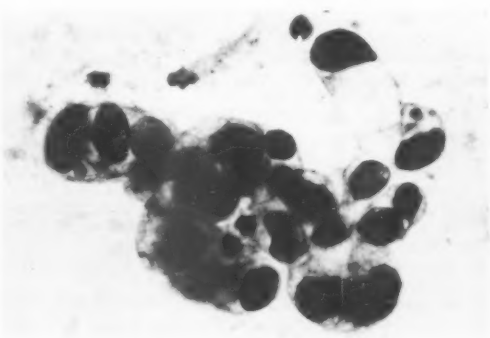

Fig. 23

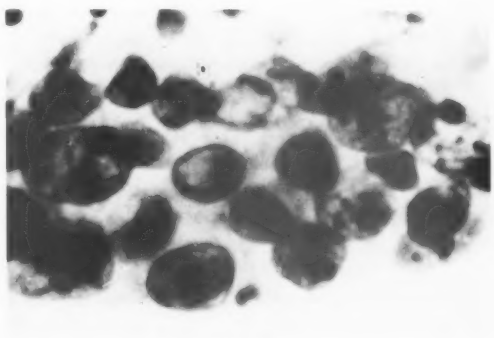

Fig. 26

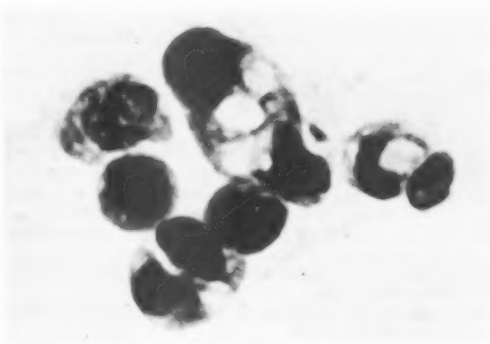

Fig. 24

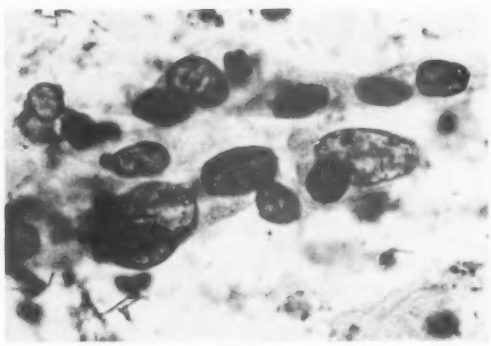

Fig. 27

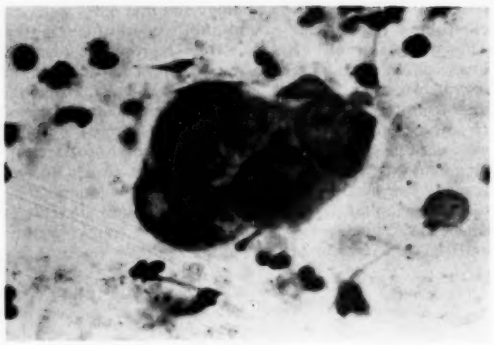

Fig. 28

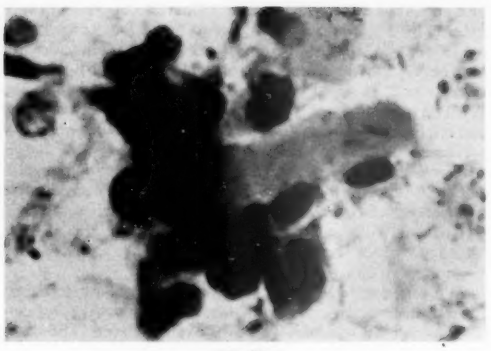

Fig. 29

peated cytological examinations of cases with chronic gastritis may achieve cancer diagnosis before infiltrative tumour growth has developed.

The gastric lesion of pernicious anaemia is histologically of a similar nature to chronic atrophic gastritis. As it appears that there exists a higher cancer morbidity in patients suffering from pernicious anaemia than in the rest of the population, repeated cytological examination of pernicious anaemia cases can again be of considerable value in the management of such patients.

It must therefore be concluded that gastric cytology is a most useful addition to the diagnostic armamentarium in the fight against gastric cancer. Out of all methods for collection of material the simple lavage method has proved itself equal in efficiency to other methods. The cells are well preserved, present in adequate numbers for the diagnosis of chronic inflammatory lesions such as chronic gastritis and for the diagnosis of cancer, be it the surface type of carcinoma or the carcinomatous tumour. It is, however, too early to judge whether or not early cancer diagnosis in the case of gastric carcinoma will alter the five year survival rates sufficiently to justify gastric cytodiagnosis, which is a very time consuming method of diagnosis that can only be practised by skilled investigators.

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THE SYMPOSIA BY CORRESPONDENCE OF ACTA CYTOLOGICA

INTRODUCTORY REMARKS

The Symposia of ACTA CYTOLOGICA are *held entirely by correspondence* and contain international discussions of scientific problems of interest to the exfoliative cytologist.

System for Selecting Subjects for Symposia: From recommendations received, the Editorial Office will draw up the list of subjects and will publish these subjects in ACTA CYTOLOGICA, under the heading FUTURE SYMPOSIA.

The final detailed program will be published in ACTA CYTOLOGICA immediately preceding the one where these topics are to be considered, under the heading, THE NEXT SYMPOSIUM.

Instructions for Authors: Each problem will be introduced by a *Main Speaker* or *Speakers.* These principal papers will then be considered by persons identified as *Discussants.* As a general rule, approximately 600 words each will be allocated for main papers and 200 words each will be allocated for the contributions of the Discussants. The Main Speakers will then be given the opportunity to make unlimited Closing Remarks.

Photomicrographs and tables may be reproduced: one full page for each principal paper and for the paper of the Discussant (maximum one-half page per contribution). The photomicrographs and tables should be submitted in glossy photographic prints, preferably in the size of 5 × 7 inches (i.e., 12 × 18 cm) and should show a proportional 10μ scale on its reverse side. *Each figure should be accompanied by a comprehensive caption.*

The Discussants are requested *to strictly restrict their contributions to the discussion of the main papers.* Discussions which are not directly related to the main paper cannot be accepted. It is suggested that the Discussants prepare their contributions in such a manner that the reader may gain the impression of an actual round table conference.

The Closing Remarks of the Main Speakers should be limited to the answering of questions raised in the discussion and to other directly related information.

The Bibliography for the papers of both Main Speaker and Discussant should be organized in the same manner as in the American Journal of Obstetrics and Gynecology, at the *end* of the paper. *Every cited opinion or publication should have a reference in the bibliography.*

Deadline for Contributions: The Editorial Office will set deadlines for each written symposium. These will include:

1. deadline for agreements to contribute.
2. deadline for main papers.
3. deadline for discussions.
4. deadline for closing remarks.

Reprints: Authors may receive reprints of their papers by ordering these reprints before the particular issue goes to press. There will be a nominal charge for reprints: $6.00 per page for the first one hundred copies, and $3.00 per page for each additional hundred.

LES SYMPOSIA PAR CORRESPONDANCE DES ACTA CYTOLOGICA

Les *Symposia par Correspondance* des ACTA CYTOLOGICA présentent des discussions internationales sur des problèmes scientifiques intéressant le cytologiste exfoliative.

Système du choix des sujets pour les symposia: En partant des propositions, et sous la rubrique: FUTURS SYMPOSIA, le bureau de rédaction dressera la liste des sujets principaux qui seront publiés dans les ACTA CYTOLOGICA.

Le bureau de rédaction établira le programme définitif et détaillé des discussions qui sera publié dans les ACTA CYTOLOGICA précédant immédiatement le symposium, sous la rubrique PROCHAIN SYMPOSIUM.

Recommandations pour les auteurs: Chaque sujet principal sera présenté par un Rapporteur Général ou des Rapporteurs. Ces mémoires principaux seront alors soumis aux Participants à la Discussion. En règle générale 600 mots seront accordés aux Rapporteurs des sujets principaux, et, 200 mots aux Participants à la Discussion. Les Rapporteurs Généraux pourront clôturer les discussions par un nombre illimité de remarques.

Des microphotos et graphiques pourront être reproduits à raison d'une page entière pour chaque sujet principal et une demi page au maximum pour les discussions. Les microphotos et les graphiques doivent être présentés sur du papier brillant, de préference dans le format 12 × 18 cm. *Chaque figure devra être accompagnée d'une legende explicative précise.*

Les membres et invités prenant part aux discussions sont invités à *limiter strictement leurs interventions aux discussions des sujets principaux.* Des discussions qui n'ont pas de rapport direct avec le sujet principal *ne pourront être acceptées.* Il est recommandé que les discussions soient rédigées d'une manière telle que le lecteure aît l'impression d'assister à une discution réelle de table ronde.

Les Remarques de Clôture du Rapporteur Général devront se limiter à la réponse aux questions soulevées dans les discussions et aux autres informations éventuelles ayant un rapport direct avec le sujet.

La bibliographie des rapports et discussions devra être rédigée de la même manière que celle de l'American Journal of Obstetrics & Gynecology et figurer à *la fin* du texte. *Chaque opinion ou publication citée dans le texte doit avoir sa réference dans la bibliographie.*

Dates limite pour les collaborations: Le bureau de rédaction, fixera des dates limites comprenaet:

1. un délai pour l'acceptation des collaborations,
2. un délai pour les sujets principaux,
3. un délai pour les discussions,
4. un délai pour les remarques de clôture.

Tirés-à-part: les auteurs pourront obtenir des tirés-à-part de leurs communications en les demandant avant la mise sous presse des ACTA CYTOLOGICA publiant leurs articles. Les tirés-à-part seront facturés: $6.00 par page de texte pour le premier cent et $3.00 pour chaque centaine supplémentaire.

DIE SCHRIFTLICHEN SYMPOSIEN DER ACTA CYTOLOGICA

Die schriftlichen Symposien der ACTA CYTOLOGICA befassen sich auf internationaler Basis mit wissenschaftlichen Problemen, die für den Exfoliativ-Zytologen von Interesse sind.

System der Thema-Auswahl für die Symposien: Die Schriftleitung stellt auf Grund von Thema-Vorschlägen eine Liste von Haupt-Themen zusammen, und gibt diese Liste unter dem Titel ZUKÜNFTIGE SYMPOSIEN bekannt.

Die Schriftleitung bereitet das Programm mit allen Einzelpunkten vor, und veröffentlicht dieses Programm in dem Heft, das dem betreffenden Symposion vorausgeht, unter dem Titel DAS NÄCHSTE SYMPOSION.

Instruktionen fur Autoren: Jedes Thema wird von einem oder mehreren Referenten behandelt. Diese Referate werden dann von Diskussions-Vortragenden besprochen. Im allgemeinen werden Referate auf etwa 600 Worte beschränkt, und Diskussions-Vorträge auf 200 Worte. Die Referenten erhalten dann die Gelegenheit, Schlussbemerkungen ohne Wortzahlbeschränkung zu machen.

Mikrophotographien und Tabellen können abgedruckt werden: eine Ganzseite kann Referenten und eine halbe Seite Diskussionsvortragenden für Abbildungen zur Verfügung gestellt werden. Die Photographien sind auf Hochglanzpapier, und möglichst in der Grösse 12 × 18 cm erbeten und soll ein proportionales 10μ Zeichen auf der Rückseite haben. *Jede Abbildung muss von einem erklärenden Untertitel begleitet sein.*

Die Diskussionsvortragenden sind gebeten, sich in ihren Beiträgen *streng an das Hauptreferat zu halten.* Diskussionsbeiträge, die sich nicht an das Hauptthema halten, *können nicht berücksichtigt werden.* Es wird vorgeschlagen, dass die Diskussionsvorträge in einem Stil abgefasst sind, dass der Leser den Eindruck gewinnt, als ob es sich um eine Diskussion am runden Tisch gehandelt hätte.

Die Schlussbemerkungen der Referenten sollen sich nach Möglichkeit auf die Beantwortung von Diskussionsfragen beschränken.

Die Bibliographie der Referate und der Diskussions-Vortäge sollen *am Schluss* der Beiträge nach dem Muster der Bibliographien im American Journal of Obstetrics and Gynecology aufgeführt werden. *Jede zitierte Ansicht oder Publikation muss eine Referenz in der Bibliographie haben.*

Termine für Beiträge: Die Schriftleitung setzt Termine für die Schriftlichen Symposien fest. Die folgenden Termine werden bekanntgegeben:

1. Termin für Erhalt der Beitrags-Zusagen,
2. Termin für Erhalt der Hauptreferate,
3. Termin für Erhalt der Diskussions-beiträge.
4. Termin für Erhalt der Schlussbemerkungen.

Sonderdrucke: Autoren können Sonderdrucke ihrer Beiträge bestellen, bevor die betreffende Ausgabe in Druck geht. Die Schriftleitung muss diese Sonderdrucke berechnen und wird einen Betrag von $6.00 pro Seite und 100 Sonderdrucke, und einen Betrag von $3.00 für jedes weitere Hundert erheben müssen.

SIMPOSIUM ESCRITO DE ACTA CYTOLOGICA

El simposium escrito de ACTA CYTOLOGICA contiene discusiones internacionales sobre problemas científicos que son de interés para el citólogo exfoliativo.

Sistema de selección de materias para el simposium: Con sugestiones recibidas, la oficina editorial confeccionará una lista de los temas más interesantes, lista que será publicada en ACTA CYTOLOGICA con dos numeros de anticipación a la fecha de su posible publicación, bajo el epígrafe de "SIMPOSIUM FUTUROS."

La Oficina Editorial confeccionará y publicará una lista detallada del programa de la discusión en el número de ACTA CYTOLOGICA immediatamente anterior a aquel en que han de ser incluidos los temas, bajo el epígrafe de: EL PROXIMO SIMPOSIUM.

Participación en el Simposium Escrito: No habrá restricción alguna sobre el número de puntos de discusión en los que cualquier autor desee participar.

Instrucciones a los Autores: Cada problema deberá ser presentado por un ponente o ponentes. Estos trabajos principales serán entonces discutidos por los comunicantes. Como regla general, se permite un máximo de 600 palabras para los trabajos principales y 200 palabras para las contribuciones de los comunicantes. Al ponente principal se le da la oportunidad de hacer rectificaciones finales ilimitadas.

Pueden reproducirse microfotografías y tablas: una página por cada trabajo principal y un máximo de media página por discusion. Las microfotografías y tablas deberán enviarse en forma de copias fotográficas amplias. A ser posible de 5 × 7 pulgadas (12 × 18 cms). *Cada figura deberá acompañarse de su correspondiente leyenda.*

Se suplica a los comunicantes *ajustar estrictamente sus comunicaciones a la discusión de los trabajos principales.* Las discusiones que no estén directamente relacionadas con el trabajo principal *no podrán ser aceptadas.* Se sugiere que los comunicantes realicen sus contribuciones de manera tal que el lector tenga la impresión de estar ante una verdadera mesa redonda.

Las rectificaciones finales de los ponentes deberán limitarse a contestar las preguntas aparecidas a lo largo de la discusión asi como a otras directamente relacionadas con el tema.

La bibliografia, tanto de las ponencias como de las comunicaciones deberá redactarse de la misma forma que figura en el American Journal of Obstetrics and Gynecology, *al final* del trabajo. *Toda opinión o publicación citada deberá tener su correspondiente referencia en la bibliografía.*

Fechas para las contribuciones: La Oficina Editorial, fijará fechas límite absolutas para cada simposium escrito. Estas incluirán:

1°. Fecha límite para acuerdo de contribución,
2°. Fecha límite para las ponencias,
3°. Fecha límite para las discusiones,
4°. Fecha límite para las anotaciones finales.

PROGRAM OF Vol. III, No. 1, 1959 SYMPOSIUM

CANCER CYTOLOGY DURING PREGNANCY

NOTE: THE SYMPOSIUM ON HORMONAL CYTOLOGY DURING PREGNANCY AND POST-PARTUM PERIOD WILL APPEAR IN VOL. III, NO. 2, 1959.

Symposium A

CANCER CYTOLOGY DURING PREGNANCY

THE SQUAMO-COLUMNAR JUNCTIONS DURING PREGNANCY.

KARL-GÜNTHER OBER
Cologne, Germany

About eight years ago the research of Epperson, Hellman, Galvin and Busby (1) caused some sensation. These authors succeeded in discovering a high incidence of carcinoma in situ during pregnancy. This same incidence could not be found after pregnancy. Thus, the question arose as to whether or not the pregnancy, per se, would cause epithelial changes that appear to be carcinoma in situ.

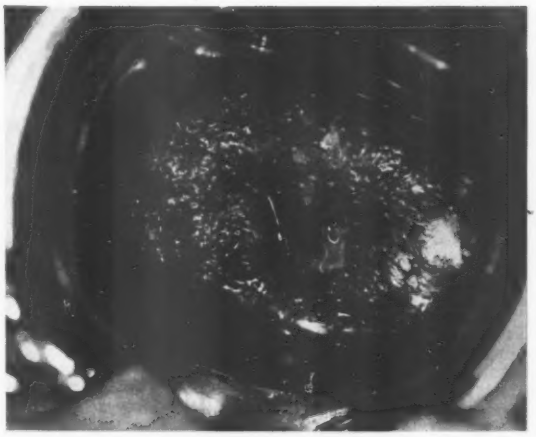

Fig. 1. Surface of the uterine cervix in a 24 year old primigravida, eight weeks before delivery of a full term baby. A scraping from the periphery of the lesion showed (cytologically) the picture of carcinoma in situ.

In the meantime, it has been shown that in pregnant women with a mean age of 27-29 years, carcinoma in situ can be detected in 3% of the cases. However, the specimens must be large enough to contain all the transitional zone between the squamous and the columnar epithelia (2). There is no doubt of the accuracy of the initial observation. Now it is also known that these changes may exist for a period of up to three years in more than 80% of the cases. This also applies to carcinoma in situ outside of pregnancy (3). How can the original question be answered in view of these facts?

These findings, which first appear contradictory, may be looked at in the following circumstances:

The cervix is a very plastic organ. It is dependent on the ovarian function and it undergoes a continuous change of form during the life of the woman (4,5). Such changes of form may be very striking during pregnancy, due to the highly altered endocrine situation. An ectropion is frequently found. This ectropion may disappear shortly after pregnancy. Thus, the fact should be considered that during pregnancy the glands of the cervix lie on the surface of the cervix. After the delivery they again retire into the cervical canal. In addition, it is known that 90% or more of all carcinomas in situ lie over the lower cervical glands. By taking a punch biopsy from the portio during pregnancy, one can be fairly sure of obtaining pathologically-altered material which would be deeply intracervical after pregnancy. In fact, by punch biopsies of the portio one examines different parts of the cervix, depending on whether the procedure is performed during or after pregnancy. Two figures may illustrate this idea. Eight weeks before delivery the portio of a 24 year old woman showed some changes, which, after guided biopsy, could easily be proved to be carcinoma in situ (Fig. 1). Four weeks after delivery, these changes could be shown no longer. However, since cervical curettage again revealed changes compatible with carcinoma in situ, conization was performed: The carcinoma in situ was situated in the distant part of the cone, i.e., completely intracervically (Fig. 2). Therefore, the morphological changes of the cervix during pregnancy may reveal epithelial changes which are usually hidden deep within the cervix.

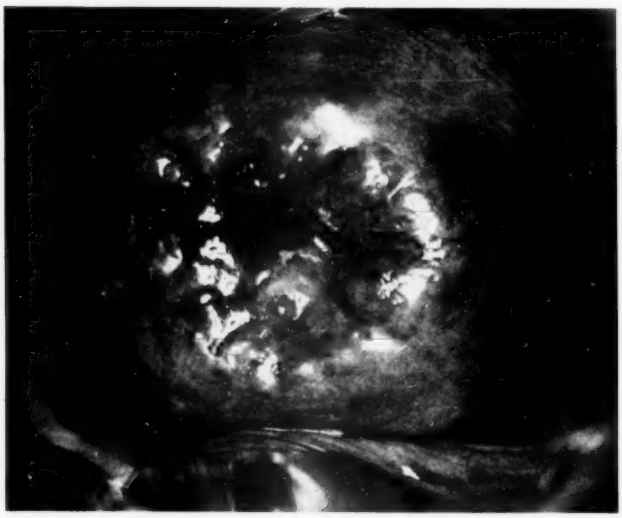

Fig. 2. The same cervix four weeks after delivery. By cervical curettage, a carcinoma in situ was again found. Conization of this cervix showed a glycogen-containing, normal squamous epithelium extending to the external os. An extensive carcinoma in situ was lying in the depth of the cervical canal.

Similar conditions may be encountered outside of pregnancy. However, the changes of the location of predilection for early lesions occur, however, over a longer period of time. Figure 3 may illustrate this.

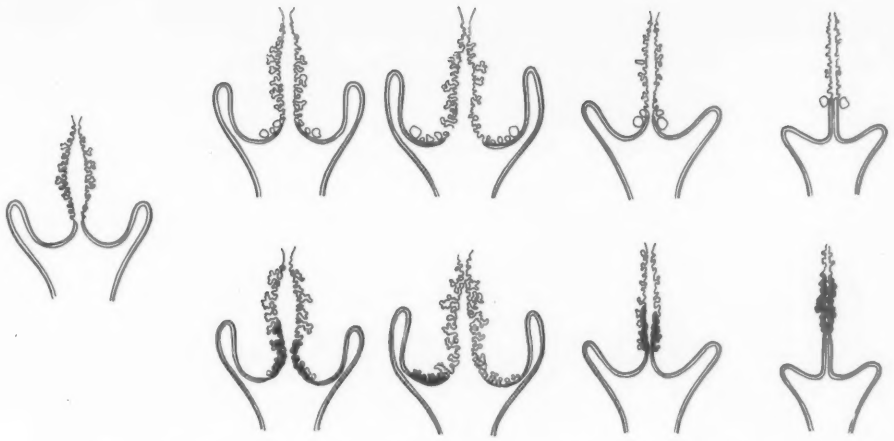

Fig. 3. The different types of cervices of the female and their significance for early diagnosis.

On the left side the ideal type of cervix is depicted. In the upper row, the first two sketches at the left show the typical behavior of the cervix in women of childbearing age. The third figure shows the typical cervix in the climacterium; the fourth picture shows the findings in the senile woman.

In younger women, the cervical glands lie more or less on the surface; in senile women, they have retired deeply into the cervical canal; in childbearing women the cervical glands lie more or less on the surface of the portio, sometimes overgrown by squamous epithelium. In the climacterium, the glands already grow into the cervical canal; while in the aged individual, one finds the epithelium far inside the cervical canal.

The lower row shows the localization of early changes expected in the columnar epithelial junction in the respective situations as sketched above. Most of the lesions are found in the lower-most groups of cervical glands.

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DISCUSSION

ALVAN G. FORAKER, Jacksonville, Florida, U.S.A.:

Changes in clinical appearance and microscopic morphology of the cervix, as noted by Ober, are paralleled by changes in the histochemical reaction pattern. In a series of biopsies from 55 pregnant and 45 non-pregnant women we found a somewhat greater evidence of succinic dehydrogenase activity in the biopsies taken during pregnancy (1). However, except for strong reactivity in decidual cells, the dehydrogenase activity showed no characteristics specific for pregnancy, but merely reflected the general increased cellular activity, including changes in epithelium at the squamo-columnar junction. Whether or not these changes, when present in extreme degree, represent intra-epithelial carcinoma, which can be diagnosed accurately, is a disputable point. This is discussed in detail in another part of this symposium. Sam Denham, my clinical conferee, has this to say: "Ectropion of the pregnant cervix is not always present. It is more common in multiparas than in primigravidas. It is wise to differentiate, in either of these two groups, an actual ectropion and the clinical pregnancy changes present in every cervix, which has been under the hormonal influence of pregnancy. It is now generally accepted that both cytological evaluation and biopsy, when indicated, are desirable in the pregnant woman. If these evaluations are made early in pregnancy and suspicion is aroused, there remains a considerable period of time, requiring close cooperation and mutual confidence between clinican and cytopathologist."

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WARREN R. LANG, Philadelphia, Pennsylvania, U.S.A.:

The extensive work of Ober and his associates in the field of cervical pathophysiology should be required reading for all serious-minded gynecologists. It is significant that Ober speaks of squamo-columnar junctions rather than a squamo-columnar junction; the meeting of the two types of epithelia on the cervix is, in the majority of cases, a mixture of columnar in squamous epithelium, rather than a line of demarcation. Although this fact is most evident by the colposcopic technique, it is confirmed by epidermization (or whatever other name) histologically. It is thought by some that atypia and preinvasive and invasive squamous cell carcinomas begin in this so-called transformation zone.

Ober rightly states that the cervix is a changing organ. During pregnancy, as before and after, columnar epithelium is often found on the portio. Some, like Ober, feel that there is an increased growth of columnar epithelium in the area of the portio during pregnancy. Is this only apparent because the columnar epithelium becomes hyperplastic and, therefore, more noticeable? Is there a true growth outward of columnar epithelium? Is there an opening-up (actual eversion) of the external os? Or is there a combination of the above? It would appear that the only way to be certain of the mechanism would be to "mark" the anatomical external cervical os and follow the limits of the two epithelia during gestation.

It seems to me that whether or not carcinoma in situ actually regresses post partum will never be completely and finally solved, since once a histological section is removed for study, who can tell what the same area will demonstrate six or nine months later after the pregnancy is over?

LOUIS J. ZELDIS and DEAN L. MOYER, Los Angeles, California, U.S.A.:

The observations of Ober are of interest in respect to a number of problems. It is perhaps questionable that they entirely account for the apparently discrepant reports cited regarding the incidence and behavior of carcinoma in situ diagnosed in pregnancy. Nonetheless, they emphasize that the apparent incidence will differ depending on the completeness with which the region of the squamo-columnar junction is examined. On the other hand, there is little doubt that the subsequent behavior of the lesions will also be influenced by the same consideration since there is little question that procedures such as ring biopsy or wider conization will destroy many lesions.

Of interest also is the role of the geographic location of the squamo-columnar junction as part of the total physiologic environment producing those histologic changes commonly seen in this region in pregnancy. These changes include edema, vascular congestion, chronic inflammatory cell infiltration and focal decidual reaction, all entirely similar to those noted elsewhere in the cervix. Particularly striking, however, is the frequent occurrence of reserve cell hyperplasia underlying both the surface and glandular columnar mucosa. This change, while seen elsewhere in the endocervical canal, is often marked at and immediately above the squamo-columnar junction. We have recently had the opportunity to examine conization specimens from a considerable number of pregnant women. Minor degrees of atypia, including dyskaryosis, are not infrequent in hyperplastic reserve cells. When present, such changes are quite uniformly more conspicuous close to the squamo-columnar junction.

NO CLOSING REMARKS

COMMENTS ARE INVITED
ABOUT ANY OF THE SUBJECTS TREATED
IN THE SYMPOSIA BY CORRESPONDENCE.

THE COMMENTS WILL BE PUBLISHED
IN THE SECTION "LETTERS TO THE EDITORS."

INCIDENCE OF CERVICAL CARCINOMA DURING PREGNANCY

JORGE CAMPOS R. de C.
Lima, Peru

Association of cervical carcinoma and pregnancy is a hard problem to solve, both as to the diagnosis and the management of these patients.

To the pathologist, the main problem is that the diagnostic criteria of cellular atypias and the morphological changes of carcinoma in situ in non-pregnant women are not necessarily valid in pregnant women. In the latter case one can frequently see morphological, cancer-like changes which return after delivery. In cases of invasive carcinoma and pregnancy, there are also diagnostic difficulties because it is not always easy to distinguish between early infiltrative carcinomas and squamous or glandular hyperplasia or atypia in pregnant women.

We cannot give figures on the percentage of pregnant women of the general population that have cervical carcinoma, since we work in a cancer institution. According to several authors' experience, however, it varies between 0.007 and 0.06 per cent, with an average of 0.01 per cent (Table 1).

We will speak here exclusively on invasive carcinoma associated with pregnancy. There were 1762 cervical carcinoma cases diagnosed in four years between June, 1952, and May, 1956, at the Instituto Nacional de Enfermedades Neoplasicas of Lima. Of these cases, eight were normal pregnancies and two tubal pregnancies, i.e., 10 cases or 0.57 per cent, which is lower than the other authors' averages.

The youngest case was a 27 year old woman. The oldest was 41 years old. The average age was 32.8 years. The number of pregnancies was two to fourteen with an average of 6.6, while the parity average was 5.7.

The age of beginning of sexual intercourse was between 13 and 19 years, with an average of 16.3 years. Meigs (10) observed that the beginning of sexual intercourse in these patients is earlier and the numbers of pregnancies are greater than in the other cases of cervical carcinoma. This observation is partially confirmed by our cases since 20.9 years is the average age in our environment, according to Barra (1), but there is no difference in the parity.

In all our cases, the first clinical symptoms of cervical carcinoma began during pregnancy. Three cases were diagnosed during the first three months, one in the fourth month and the other four in the last three months of pregnancy.

When the diagnoses were made, seven cases were in clinical Stage I, two in Stage II and one in Stage III.

However, in spite of the fact that most cases were diagnosed in the first stages, the mortality has been great. We know of six cases in which four died of carcinoma and the other two have not as yet been observed for a five year period.

Table I

Occurrence of Cervical Carcinoma in Pregnant Women

Authors	Number of Pregnant Women	Cervical Carcinoma Number of Cases	%
Willson	39.719	6	0.015
Ward	36.274	10	0.027
Hirst	46.806	5	0.010
Eastman	41.451	3	0.007
Danforth	20.444	3	0.014
Johnson and Weinfurtner	29.394	12	0.04
Thornton and Co-workers	8.450	5	0.059
Hayden	81.806	12	0.015
	304.344	56 Average Percentage	0.187

Table II

Occurrence of Pregnancy in Patients with Cervical Carcinoma

Authors	Number of Cases with Cervical Carcinoma	Number of Cases Pregnant No.	%
Maino and Mussey	3.570	26	0.7
Jensen	1.168	22	1.9
Machado	500	6	1.2
Sadugor and Co-workers	4.652	124	2.7
Johnson and Weinfurtner	788	12	1.5
Hirst	905	18	1.9
Thornton and Co-workers	280	5	1.7
Hayden	485	12	1.2
Este report	1.762	10	0.6
	Total: 14.110	235 Average Percentage	1.6

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Cancer of the cervix complicated by pregnancy refers to patients who are pregnant or have been pregnant within three months of the time when treatment of the cancer is begun.

A survey of the records of 3008 cervical carcinoma patients treated at Roswell Park Memorial Institute in the years 1935-52 revealed 33 cases associated with pregnancy. This gives an overall incidence of 1.1%. In two successive series of consecutive clinic cases, personally observed, the incidence was higher. In the Boston area (at the Massachusetts General Hospial, Free Hospial for Women, Peter Bent Brigham, and Pondville Hospital) in 1954-56, this complication was encountered seven times in 207 patients. In Buffalo at R.P.M.I. in 1957-58, it was encountered eight times in 208 cases, or 3.6%. The latter figure is probably more accurate and is a reasonable estimate of the frequency of this complication in clinic patients in the northeastern United States in recent years.

In the recent Boston-Buffalo series, seven patients were Stage I, three were Stage IIa, one was Stage IIb, three were Stage III and one was Stage IV. The relative frequency of the stage of disease in all patients in these series was 31%-I, 29%-IIa, 19%-IIb, 15%-III and 6%-IV.

The age range was from 26 to 41 years. The average age in both Boston and Buffalo was 34 years.

We may conclude that pregnancy complicates cancer of the cervix in approximately 3.6% of the cases. The lesion tends to be of about the same clinical extent, but the patient is younger than in the overall group.

THOMAS A. SLATE
San Diego, California, U.S.A.

The incidence of carcinoma of the cervix in pregnant women varies with several basic factors, namely, age, social status, racial and religious differences and percentage of the population previously screened. In general, the incidence of carcinoma of the cervix is higher in the indigent, Negro and Mexican patients and is much lower in the Jewish population.

This report is based on a comparison between our original study of 5,935 private, pregnant patients (1950-1955) (1) and a current study of routine smears from 4,109 private, pregnant patients and 1,385 indigent clinic, pregnant patients (1956-1958). The results of 6,079 non-pregnant private patients, screened during 1956-1958, will be compared with the pregnant group. The indigent patients studied are being screened for the first time and include a large number of Mexican women.*

RESULTS

Detections from pregnant patients studied from 1956-1958, revealed five premalignant or borderline lesions, 12 carcinomas in situ (2.9 per thousand), and two invasive carcinomas (0.48 per thousand). The non-pregnant group presented 15 premalignant or borderline lesions (2.5 per thousand), 40 carcinomas in situ (6.6 per thousand) and six invasive carcinomas (0.98 per thousand or one per 1,013). Only 23 carcinomas in situ were detected from patients below age 34, giving a yield of 3.7 per thousand, which compares favorably to the yield of 2.9 per thousand in pregnant patients below age 34.

Table II shows the disposition of patients having abnormal smears without histologic studies. In the Class III-B category of the pregnant group nine are still pregnant and being followed, and seven were lost to follow-up studies. We would expect the nine being followed to yield five or six carcinomas in situ. An addition of only five carcinomas in situ would give a yield of 4.1 per thousand, which is slightly greater than in the non-pregnant group of similar age. The two cases having repeated Class IV and V smears are expected to show at least carcinoma in situ, and thus were included in our statistics.

*San Joaquin General Hospital, French Camp, California. Under the direction of D. C. Harrington, M.D., Jack Rowland, M.D., Edward B. Tonge, M.D. and with the cooperation of the pathologist, Harry J. Schneider, M.D.

TABLE I. COMPARISON OF HISTOLOGIC FINDINGS IN VARIOUS AGE GROUPS OF PRIVATE PREGNANT AND NON-PREGNANT PATIENTS WITH ATYPIAS WHICH WERE DETECTED BY ABNORMAL SMEARS

	4,109 PRIVATE PREGNANT PATIENTS						6,079 PRIVATE NON-PREGNANT PATIENTS					
Ages	Premalig. Dysplasia	Per 1,000 Exam.	In situ Ca.	Per 1,000 Exam.	Invasive Ca.	Per 1,000 Exam.	Premalig. Dysplasia	Per 1,000 Exam.	In situ Ca.	Per 1,000 Exam.	Invasive Ca.	Per 1,000 Exam.
19-23	1		2		1 (20 yrs.)		4		0		0	
24-28	2		4				4		7		2	
29-33	2		1				4		14		3	
34-37	0		5		1 (37 yrs.)		1		11		1	
38-42	0		0				2		8		0	
Total	5	1.2	12*	2.9	2	.48	15	2.5	40	6.6	6	.98
Youngest age	19		20		20		21		25		24	
Oldest age	31		33		37		39		40		34	

All minor atypias are excluded from this study. Twenty-three of the non-pregnant patients with carcinoma in situ were under 34 years of age with a yield of 3.7/1000. All pregnant patients were under 34 years of age, with a yield of 3.9/1000.

*Two of these cases had definite evidence of carcinoma in situ by smears, but are awaiting histologic confirmation.

TABLE II. DISPOSITION OF PRIVATE AND INDIGENT PREGNANT PATIENTS WITH ABNORMAL SMEARS WITHOUT HISTOLOGIC FOLLOW UP

SMEARS	NO. OF PATIENTS	PRESENT STATUS		
		STILL PREG.--BEING FOLLOWED	POSTPARTUM--AWAITING BIOPSY	LOST TO FOLLOW UP
Private Patients				
III-B	16	9	0	7
IV	1*	1	0	0
V	1*	0	1	0
Indigent Patients				
III-B	7	1	0	6
IV	3	3	0	0

*Both cases with Class IV and V smears were repeated during pregnancy and definitely suggest carcinoma in situ.

Table III outlines a summation of our combined studies totaling 10,044 private, pregnant patients. The average age was 25.6 years in comparison to 31.9 years in the non-pregnant group. The yield from this group was 1.5 per thousand premalignant or borderline lesions, 2.5 per thousand pre-invasive carcinomas, and one per 2,008 invasive carcinomas.

TABLE III. INCIDENCE OF CERVICAL CARCINOMA IN 10,044 PRIVATE, PREGNANT PATIENTS COMPLIED FROM THE ORIGINAL AND PRESENT STUDIES

ORIGINAL GROUP	NO. OF PATIENTS	AVERAGE AGE	PREMALIGNANT DYSPLASIAS (major Atypias and Borderline lesions)	AVERAGE AGE	IN SITU CA.	AVERAGE AGE	INVASIVE CA.	AVERAGE AGE
(1950-1955)	5,935	27	10	27.7	13	26.9	3	32.6
PRESENT STUDY (1956-1958)	4,109	24.3	5	27.2	12	28.5	2	28.5
TOTAL	10,044	25.7	15 (1.5/1000)	27.4	25 (2.5/1000)	27.7	5 (1/2008)	30.6

TABLE IV. ANALYSIS OF HISTOLOGIC FINDINGS DETECTED BY ABNORMAL SMEARS (CLASS III-B, IV, AND V) FROM ROUTINE SCREENING OF 1,385 INDIGENT PREGNANT PATIENTS*

AGES	PREMALIGNANT DYSPLASIAS (Major Atypias and Borderline Lesions	CARCINOMA IN SITU	INVASIVE CARCINOMA
18-23	1	3	0
24-28	1	2	0
29-33	0	2	1
34-37	0	2	1

The average age of entire group: 24.37 years.

*San Joaquin Valley Hospital, Stockton, California.

An analysis of 1,385 indigent, pregnant patients screened revealed two premalignant or borderline lesions, nine carcinomas in situ (6.5 per thousand), and two invasive carcinomas. If three additional cases of carcinoma in situ being followed with Class IV smears were added, we would have a more accurate incidence of 8.6 per thousand.

COMMENTS

The incidence of carcinoma in situ in private, pregnant patients studied varied from 2.5 to 4.1 per thousand, while that of invasive carcinoma was one per 2,008.

In comparison, the indigent, pregnant patients revealed an incidence of 6.5 per thousand preinvasive carcinomas, with a potential yield of 8.6 per thousand. The incidence of invasive carcinoma in this small group was one per 692 patients. This supports the theories that incidence of carcinoma, both in situ and invasive, is greater in the indigent population.

We have attempted to follow pregnant patients with Class III and IV smears only, with repeated smears until 6 weeks or more postpartum when a cold cone or an adequate biopsy is done. This eliminates the present argument of questionable diagnosis of carcinoma in situ during pregnancy. Patients with Class V smears and/or suspicious lesions had four quadrant biopsies during pregnancy to rule out invasive carcinoma.

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PETER STOLL

Heidelberg, Germany

During a period of 21 years (1930-1951) we have seen invasive carcinoma of the uterine cervix, during pregnancy or in the early postpartum phase, 21 times in a total of 1828 cases of cervical carcinoma (1.15%). The age of the patients was from 23 to 42 years. Taking out of the 1828 cases of carcinoma of the cervix only those ranging between 23 and 42 years, there remain 502 cases (27.25%), of which 21 were combined with pregnancy. From those patients within the childbearing age the average age was:

1. cervical carcinoma without pregnancy: 32.9 years.
2. cervical carcinoma with pregnancy: 32.4 years.

Within this age group the incidence of pregnancy with carcinoma of the cervix is 4.2%.

It does not seem justified to compare these features with the number of patients delivered or treated with abortion during the given time, because in our area nearly all cases of cervical carcinoma are admitted to our hospital, while only about 40% of all deliveries or abortions are handled under our supervision.

In regard to the international stage of cervical carcinoma, we found the following:

	I	II	III	IV	Compared in %
During pregnancy	6	10	4	1	29:47:19:5
Without pregnancy	206	393	180	50	25:47:22:6

Of the 21 patients, 6 had 6 gestation periods before the carcinoma developed, 2 had 5, 4 had 4, 6 had 3, 2 had 2 gestations and 1 has had only one abortion.

Treatment consists of radical surgery in most cases. The cure rate is as follows:

	Cases	+	observation under 2 years	cured	not followed
First third of pregnancy	5	1	1	3	
Second third of pregnancy	5	2	2	-	1
Third third of pregnancy	5	3	1	-	1
Post partum	6	5	1	-	

Hartl-Göttingen has found within 16 years and 676 cervical carcinomas, 4 combined with pregnancy, which is 0.59%. Our figures are 21 out of 1828 which is 1.15% and corresponds to Danforth with 1.0% and 1.8% and the figures from the General Hospital, Louisville with 1.54%.

The total number of patients delivered in our hospital during 1930-1951 is 26,726, of which 21 cases or 0.08% were combined with carcinoma of the cervix. This is 1 in 1274 deliveries. In the world literature these figures range from 0.03% up to 0.56% (Peham-Amreich, Danforth, Johnson and Weinfurtner). As already pointed out, the difference may be a matter of selection, given by the modus of admission to a special hospital in the area. Taking in account that:

1. the number of deliveries and abortions in our hospital during the last 21 years is about 50,000 and this is only 1/2 of all gestations in our area, the number of gestations on our population can be estimated at 100,000.

2. there were seen 502 cases of cervical carcinoma in patients under 42 years of age, 21 of those were pregnant. Supposing that all cases of carcinoma of the cervix were referred to us, the general incidence of carcinoma of the cervix with pregnancy can roughly be estimated, and would be 21 in 100,000 or 0.021%.

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DISCUSSION

GEORGE J. ANDROS, Philadelphia, Pennsylvania, U.S.A.:

I can see no logical reason why the incidence of carcinoma of the cervix during pregnancy should differ materially in a particular population segment from the incidence in the non-pregnant state -- when similar age groups are compared. The true incidence figure will be determined only when all adult, pregnant females are screened "routinely" by means of cervical-endocervical smears,

and when the investigative follow-up of significant cytological abnormalities discovered during gestation is carried out as thoroughly as when no pregnancy is present.

On the Clinic Service at the Temple University Medical Center we carry out cold-knife conization biopsy of the cervix during pregnancy whenever cytological examinations point strongly to the possibility of a maligancy being present.

In the last 1000 pregnant women screened cytologically, subsequent conization biopsies (during pregnancy) revealed nine cervical malignancies. Seven of these were in situ lesions and two showed invasion (Stage I). One other patient was found to have non-invasive malignancy following the first cytological examination carried out three weeks after surgery for tubal pregnancy. Our pathologists use the same histological criteria for diagnosing in situ carcinoma during pregnancy as in the non-pregnant state.

The incidence of in situ malignancy without pregnancy in our similar, predominantly Negro clinic population is 9.8 per 1000 patients screened. The ages of the patients having non-invasive lesions associated with pregnancy ranged from 25 to 41 years (mean 32.5). The two patients with invasive cancer were ages 37 and 39. Approximately 25 percent of pregnant patients screened were under 25 years of age.

RONALD R. GREENE, Chicago, Illinois, U.S.A.:

Our experience with invasive carcinoma during pregnancy is too minimal to warrant comment. Also, unfortunately, we have no valid figures on the incidence of preinvasive carcinoma during pregnancy, as our data includes many cases referred for screening because of a suspicious appearing cervix, as well as pathological material referred to us because of its interest. We do not agree with Campos' comment, "the diagnostic criteria of cellular atypias and morphological changes of carcinoma in situ in nonpregnant women are not necessarily valid in pregnant women." We believe that if the criteria are met, such diagnoses are valid whether the woman is or is not pregnant. Recent articles by Hamperl, Kaufman and Ober; Marsh and Fitzgerald; Slate; Kawecki; Nuovo; and Greene and Peckham have presented evidence that a lesion diagnosed as preinvasive carcinoma during pregnancy persists as such in the vast majority of instances after the termination of the pregnancy. The latter authors have shown that the "persistance" rate was the same in a group of nonpregnant patients as in those pregnant at the time of the original diagnosis. Peckham and Greene have also shown that the fate of lesser abnormalities of the cervical stratified squamous epithelium was the same whether the woman was or was not pregnant at the time of the original diagnosis.

EMMERICH von HAAM, Columbus, Ohio, U.S.A.:

Dr. Campos stresses, as a main problem, the fact that the diagnostic criteria of carcinoma in situ for non-pregnant women are not necessarily valid in pregnant women and that it is not always easy to distinguish early infiltrative carcinoma from squamous or glandular hyperplasia in pregnancy. He, as well as Ruth Graham, agrees that pregnant women with cancer of the cervix are in a younger age group than non-pregnant women. Slate's study clearly showed that the incidence of carcinoma of the cervix in pregnant women is greater among the indigent population, an observation with which we agree wholeheartedly.

EDMUND SCHÜLLER, Vienna, Austria:

A survey of the records of 3,186 patients with cervical carcinoma treated at the Second University Department of Obstetrics and Gynecology of Vienna during the years 1925 - 1953, revealed 23 cases associated with pregnancy (0.7%). The average age was 33.2 years and all cases were multipara (14 were Stage I and Stage II). The treatment consisted of radical surgery in all cases and in cases of advanced pregnancy were combined with classical Caesarean section.

The cure rate is as follows: (observation more than five years)
First and second trimesters of pregnancy - 10 cases cured.
Third trimester of pregnancy, all six cases (five Stage I, and one Stage II) died soon after the initial diagnosis and therapy of a recurrent carcinoma.

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CLOSING REMARKS

JORGE CAMPOS R. de C., Lima, Peru:

The very interesting observation of Slate and von Haam that cervical carcinoma in pregnant women is more frequent in indigent people coincides with our experience at the Instituto de Enfermedades Neoplasicas, in Peru.

We see almost 450 new cases of cervical carcinomas every year. This figure is very high if we consider that Lima has 1,200,000 inhabitants and the entire country has about 10 million. In such cases, we seldom see a person from the good income group. This situation is repeated when cervical carcinoma is associated with pregnancy.

Greene states "a lesion diagnosed as preinvasive carcinoma during pregnancy persists as such in the vast majority of instances after the termination of the pregnancy." Although this aspect of the problem does not seem to fit into the chapter "Incidence of Cervical Carcinoma During Pregnancy," we would like to say that there are two contradictory criteria concerning this matter, as Foraker states in another part of this Symposium. Our observations, as those of Vokaer, Epperson, Nesbitt, Hillman and Foraker, are opposite Greene's. It is probable that there could be certain differences in diagnostic criteria rather than in diagnostic mistakes. We think that the observations made by various authors in many cases of cervical lesions resembling carcinoma in situ in pregnant women which disappear post partum could not have always been due to misinterpretation. Besides, such observations coincide with those of the cytologist who finds different cytological patterns during pregnancy, including in some instances atypical cells which disappear in the postpartum period.

PROGNOSIS OF CERVICAL CARCINOMA DURING PREGNANCY AS COMPARED TO THE PROGNOSIS OF CERVICAL CARCINOMA IN NON-PREGNANT WOMEN

WERNER BICKENBACH AND HANS-JÜRGEN SOOST
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Forming a point of view on this problem is difficult since the occurence of cervical carcinoma during pregnancy, fortunately, is a rare phenomenon, even at larger clinics where observers see only relatively few cases. A comparison of the total number of these cases observed in the course of many years, with the statistical results of cases of cervical carcinoma during the same period, provides only an indefinite basis for the prognosis. For a critical opinion, one must, in every case, take into consideration the stage of the carcinoma, the age of the pregnancy and the method of treatment, as well as the improvement of the therapeutic results during the course of the years. Therefore, only similar cases can be subject to comparison. Since these conditions can be fulfilled only to a limited extent, the results must be viewed with caution. This also applies to the following discussion of our own results.

During the years 1934-1952, 6,983 non-pregnant women with cervical carcinoma were treated at the First Universitats-Frauenklinik in Munich. The relative cure rate after 5 years was 45% (Stage I = 70.0%, Stage II = 57.3%, Stage III = 34.3%, Stage IV = 25.8%.

During the same period we observed 28 cases of cervical carcinoma in pregnant women: six cases in the first trimester, eight cases in the second trimester, and four cases in the last trimester of pregnancy. In seven women the carcinoma was discovered and treated immediately post partum and in three cases post abortum.

Histology showed 27 cases of squamous carcinoma and one case of adenocarcinoma of the uterine cervix.

The results of therapy are presented in Table I.

Table I: Five Year Cure Rates of Cerical Carcinoma Occurring During Pregnancy

Stage of Pregnancy	Number of Cases	5 Years Survival (Cured)	Not Cured (Deceased)	Relative Cure Rate
First Trimester	6	6 (3 Stage I, 3 Stage II)	-	12:18 = 66.6%
Second Trimester	8	4 (3 Stage I, 1 Stage II)	4 (3 Stage II, 1 Stage III)	
Third Trimester	4	2 (1 Stage I, 1 Stage II)	2 (1 Stage II, 1 Stage III)	
Cases treated post partum or post abortum	10	1 (Stage I)	9 (6 Stage II, 3 Stage III)	1:10 = 10.0%
Total	28	13	15	13:28 = 46.4%

Table I shows that the prospects of cure of cervical carcinoma in the pregnant group are, if anything, better than in the non-pregnant group. We doubt if the higher cure rate of 46.4% can be considered of any significance in view of the small number of cases. The results appear to be more favorable in the earlier months of pregnancy, although other circumstances (stage of carcinoma, method of treatment) must be taken into consideration. The prognosis shows a very marked deterioration after the termination of pregnancy. Only one case of Stage I carcinoma was cured; all other patients in whom treatment commenced post partum or post abortum died. The primary mortality was nil.

The early recognition of carcinoma in pregnant women appears to be even more important than in non-pregnant cases. Of eight cases of Stage I carcinoma (seven pregnant, one post partum) all survived. In the 15 cases of Stage II carcinoma, five patients treated during pregnancy survived, while four treated during pregnancy died and all patients treated only after delivery died. All five cases of Stage III carcinoma (two pregnant, three post partum) died. We did not see any cases of Stage IV carcinoma during pregnancy.

On looking at the cure rates from the point of view of the therapy applied, it would appear as if operative treatments (Wertheim or Wertheim with subsequent x-ray therapy) with a relative cure rate of 66.6% were far superior to the irradiation treatments (combined radium x-ray therapy only, or caesarean section associated with Porro's operation and subsequent radium x-ray therapy) with only 31.25% cured. However, a close scrutiny of the material shows that conditions in the two groups are so different that they cannot be readily compared with one another. Cases with apparently good prognoses were operated on while others were subjected to irradiation treatment.

The patients treated by surgery consisted of six cases of Stage I, two cases of Stage II, and only two postpartum cases. The patients treated by irradiation consisted of one case of Stage I, five cases of Stage II, two cases of Stage III and eight postpartum cases of which three cases were Stage III carcinoma.

In our experience, results are particularly bad when pregnancy is terminated by caesarean section associated with Porro's operation and subsequent irradiation with radium and deep x-ray treatment. Three out of four patients died. This unfavorable course may be due to the fact that in these cases postpartum changes made their appearance during therapy.

We do not believe that pregnancy retards the rate of growth of the carcinoma to any considerable extent. This we find substantiated by the fact that the number of advanced stages of carcinoma rises with the advancing pregnancy. However, one may be certain that pregnancy does not lead to an increased rate of growth of the carcinoma.

The favorable cure rate appears to be due primarily to the fact that this cancer responds well to therapy, particularly when it occurs during the first half of pregnancy. This applies to surgical treatment but may also apply to irradiation therapy.

The following deductions can be drawn:

1. The prospects for curing cervical carcinoma during pregnancy are more favorable the earlier the cancer is discovered, and, seemingly, the less advanced the pregnancy happens to be. Therefore, despite the rarity of the condition, one should always bear in mind the possible existence of a carcinoma in cases of bleeding during pregnancy. One should not be satisfied with the diagnosis of bleeding due to an abortion or a placenta praevia without having done a speculum examination in every case, and, if indicated, following this with other diagnostic procedures.

2. Since early cervical carcinoma during pregnancy often does not produce any obvious symptoms and since it shows such extraordinary rate of growth during the puerperium, every woman who has delivered should be subjected to a gynecological and speculum examination before discharge from the hospital. Furthermore, a routine examination should be done six weeks post partum, since it is often only then that a definite opinion can be formed concerning the widespread lacerations near the external cervical os.

3. In view of the good prospects of curing cervical carcinoma during pregnancy, as compared with the particularly bad results post partum, we now attempt to maintain a pseudo-pregnancy by hormone administration until the treatment of the carcinoma has been completed in those cases in which pregnancy has been terminated by abortion or delivery.

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GENEVIEVE DALIAN, ARLETTE SIMATOS AND VIOLETTE M. NUOVO
Paris, France

This investigation has been restricted to epidermoid carcinoma of the cervix. Glandular carcinoma has been excluded.

I. INVASIVE CARCINOMA

A. Non-pregnant women

From October, 1949, to January, 1958, vaginal smears were obtained from 25,681 non-pregnant women. Three hundred eighty-eight cases of invasive carcinoma of the cervix were found within this group and were subsequently treated. Because the specimens are sent to us from numerous clinics, complete follow-up is impossible on every patient. However, we have been able to observe 106 of these patients after treatment:

80 had surgical treatment.
26 had radium therapy.
Within this group of 106 patients:
8 died (7 had surgical treatment)
(1 had radium therapy).
4 had clinical recurrence and Class IV smears
(all had surgical treatment).
5 had Class IV smears one to four years after treatment
(3 after surgery had been performed)
(2 after radium therapy).
4 Class III smears were found a year after treatment
(2 had surgical treatment)
(2 had radium therapy).

The remaining 85 patients who were followed maintained good health. Their smears have been negative from a few months to eight years.

Time since treatment	Good Health with Negative smears	Good Health with Cl. III smears	Good Health with Cl. IV smears	Clinical recurrence with Cl. IV smears	Death
Less than a year	30		2		6
1 year	22	4	2	4	
2 years	11				1
3 years	10				1
4 years	5		1		
5 years	2				
6 years	2				
7 years	2				
8 years	1				
	85	4	5	4	8

The percentage of recurrence is 11.3 since there were eight deaths and four clinical recurrences. The Class III and Class IV smears with no symptoms have not been included because the ultimate results of these cases are uncertain. We find it advisable to continue observation of the false-negative and false-positive smears.

1. Among the 55 false-positive smears:
13 had negative biopsies. No smears were taken afterwards.
9 had no pathological examinations but the repeated smears were negative.
15 had negative biopsies or conization followed by negative smears.
18 had suspicious biopsies with subsequent negative smears.
2. Among the false negatives:
An immediate repetition was requested in four cases because of the presence of Trichomonas vaginalis in three cases, and in the fourth there was an insufficient amount of cells. In two cases, the slides should have been Class III.
Four cases were Class II:
1 contained an error in the slides.
2 were cases of intra-epithelial cancer.
1 was an invasive cancer which was detected by biopsy.
The operative specimen was negative.

B. Pregnant Women

From October, 1949, to January, 1958, vaginal smears were obtained from 6,652 pregnant women.
Twenty-five had invasive carcinomas of the cervix.
Twenty were followed after treatment:
17 had surgical treatment.
3 had radium therapy.
The mortality rate was zero for this group:
1 had a clinical recurrence 4 years after surgery; subsequent irradiation.
1 had a Class IV smear one year after surgical treatment.
1 had a Class III smear 2 1/2 years after radium treatment.
The remaining 17 cases are alive and well and continue to have negative smears.

Further analysis of actual recurrence within this group reveals a percentage of only five.

As in the cases of non-pregnant women, we have been observing what occurs in the false-positive smears of pregnant women. There have been no false-negative smears.

Two of the Class IV cases were found to have false-positive smears. One of these cases was classified three times as belonging to Class III and four times as belonging to Class IV (at various times during pregnancy). One month after delivery the smears were still consistent with Class IV, and conization of the cervix was performed. No evidence of abnormal tissue could be found on the sections of the specimen at this time. In the three months following conization, the smears continued to be of the Class III type. No further treatment was instituted, and three years later the smears still were consistently negative. This case still remains somewhat difficult to interpret. We have reviewed the smears and still believe them to be consistent with a diagnosis of malignancy, in spite of the negative pathology report. No explanation of our erroneous diagnosis can be advanced.

The second case was classified as Class IV in one instance during pregnancy and as Class III at four further examinations. A biopsy was thereupon performed and showed epidermization. The smears eventually returned to normal and remained normal after delivery.

Apart from these cases one patient had a Class IV smear. She had a biopsy showing a suspicious dysplasia.

II. CARCINOMA IN SITU:

A. Non-pregnant women

Among the 25,681 patients who had vaginal smears, 131 were found to have carcinoma in situ.

Thirteen cases were not followed.
One hundred and fifteen cases were treated by conization, amputation of the cervix, hysterectomy or radium therapy:
In 32 cases, there was no follow-up after treatment.
Eighty-three patients were followed:
1 had Class IV smears seven months after conization.
1 had Class III smears one year after conization.
1 was Class III two years after conization. An amputation of the cervix revealed a dysplasia. The patient has not been subsequently followed.
1 had Class III smears five months after conization. She then had an amputation of the cervix which still showed an intra-epithelial carcinoma; she was not followed afterwards.
3 exhibited positive smears during the months following conization and then had amputations of the cervix. (Two of them showed carcinomas in situ; in the third case no lesion was evident.) The smears have remained negative from one to three years.
2 had positive smears a year after amputation of the cervix. One received radium treatment and is alive and well. The smears have remained negative. The other had a biopsy which showed an invasive carcinoma.

It is our impression that even an extensive conization may not always be adequate treatment, as evidenced by nine of these patients who had consistently positive or suspicious smears after conization. It is possible, on the other hand, that a certain quantity of abnormal cells may be present on the smears when taken shortly after conization. Because of the still positive smears found in five cases of conization, amputation of the cervix was performed. The pathological report was as follows: in three cases evidence of carcinoma in situ was found in the operative specimens; one revealed only a dysplasia and no lesions were seen in the fifth case. In four of these five cases the amputation was performed in the months following the conization. The amputation which disclosed dysplasia was performed two years after conization.

Only one case of these 131 carcinomas in situ became invasive. This patient had, after positive smears, an amputation of the cervix showing a carcinoma in situ. Three months later the smears continued to be positive and the colposcopy was abnormal. The subsequent biopsy confirmed an invasive

carcinoma. She then had radium therapy. A year later the smears became positive again, and radiotherapy was instituted. She now has Class II smears.

This may indicate a case of carcinoma in situ becoming an invasive carcinoma. Or perhaps the pathological examination of the amputation was not complete and missed an invasive point.

Thus, if the first supposition is the correct one, the percentage of carcinoma in situ becoming invasive carcinoma in non-pregnant cases would be 0.7%.

Three cases were followed without treatment on the basis of vaginal smears. Because the smears repeated after biopsy did not demonstrate further evidence of cancer, these patients were not treated:

2 had suspicious smears one month and five months after biopsy.
1 had negative smears one year after biopsy.

These three cases might be considered as reversible lesions, representing a percentage of 2.2.

B. Pregnant Women

Among the 6,652 pregnant women who had vaginal smears, there were 26 cases of carcinoma in situ plus three cases which became invasive carcinoma:

One was not followed. Twenty-eight were followed.
Nineteen were treated and followed:
16 were asymptomatic and had negative smears.
3 had positive smears in the follow-up:

1. One case had a hysterectomy a year after an invasive carcinoma was found. The smears then became negative. Four years after the hysterectomy the smears were Class IV and she was treated with radium and radiotherapy.
2. A patient had positive smears during the whole pregnancy. Four months after delivery an extensive conization showed a carcinoma in situ. She again had positive smears a year later during a second pregnancy. A cesarean section and a hysterectomy were performed. An invasive carcinoma was discovered in the operative specimen. A year later she is in good health and has negative smears.
3. The third case involves a patient who had positive smears and a carcinoma in situ as revealed by biopsy. During pregnancy she had a miscarriage. Six months later she had positive smears and a very adequate biopsy which was negative. The smears remained positive and a conization performed four months later demonstrated an invasive carcinoma. A hysterectomy was subsequently performed at which time an invasive carcinoma was discovered. Her smears have remained Class I during a four year period. This case may be considered as doubtful since the biopsy, which was performed essentially for the purpose of diagnosis of an intra-epithelial cancer, may have been taken at the wrong place.

In cases of pregnant women, it is evident that three out of the 29 cases of carcinoma in situ eventuated in invasive carcinoma. This represents a percentage of 10 or, if the last case is excluded, which seems more logical, 6.8, which is extremely high.

Nine cases had a biopsy which gave evidence of intra-epithelial carcinoma during pregnancy and had received no treatment. Observation was continued:

2 of them had other biopsies after delivery, which still showed carcinoma in situ
7 have been followed by means of smears only:
6 continue to have positive smears.
1 had negative smears.

This last case seems to be a case of a reversible lesion. It represents four per cent of all the cases carcinoma in situ during pregnancy. Since it is still accepted by some clinicians that the reversibility of such lesions is due to pregnancy, we will compare these results with the results obtained in cases of carcinoma in situ in non-pregnant women.

	Number of cases	Invasive carcinoma		Number of cases followed	Recurrence			Cl. III or Cl. IV after treatment	Cancer in situ		Recurrence = becoming invasive carcinoma		Reversibility	
		No.	%		Deaths	Clinical	%		No.	%	No.	%	No.	%
Pregnant women	6,665	25	0.4	20	0	1	5.	3	26 + 3 included an invasive Ca chart 131	0.4	3	10	1	3.4
Non-pregant women	25,681	388	1.5	106	8	4	11.3	13		0.5	1	0.7%	3	2.2

CONCLUSION

1. One observes from the preceding chart that among the cases studied, invasive carcinoma was five times more frequent in non-pregnant women than in pregnant women. The only instances of death among these patients occurred in the group of non-pregnant women, and the percentage of recurrence is much higher among the non-pregnant women.

2. In the cases of carcinoma in situ the percentage of cases is essentially the same whether the patient is pregnant or not. In pregnant women the percentage of carcinoma in situ evolving into invasive carcinoma appears to be ten times higher than in non-pregnant women.

3. In spite of this fact, carcinoma in situ is apparently the same lesion whether the patient is pregnant or not, and in both cases the proportion of reversibility seems approximately the same.

HERBERT E. NIEBURGS

New York, New York, U.S.A.

The significance and management of invasive cervical carcinoma during pregnancy has been extensively described and further elaboration does not seem to be within the scope of this topic. There is, however, a diversity of opinion regarding the approach to carcinoma in situ of the cervix when found during pregnancy. Although no specific epithelial changes in the cervix occur during pregnancy, hyperplasia and metaplasia of the endocervical glandular cells occurs more often during pregnancy than in the non-pregnant woman. In addition, there is increased proliferation of the stratified squamous epithelium. Sometimes marked basal cell proliferation extending throughout the epithelium occurs. These cell types, particularly when associated with slight atypia, possibly due to infections, may be confusing. For this reason a diagnosis of carcinoma in situ during pregnancy is often not made, while the identical cellular or histologic change in the non-pregnant woman would permit such a diagnosis.

It is regrettable that there is no unanimity of opinion as to what constitutes a "carcinoma in situ" either from the cytologic or histopathologic standpoint. Therefore, the evaluation of reported carcinoma in situ lesions which have regressed post partum and comparison with those which have persisted is difficult. Furthermore, the possible removal of a lesion by biopsy has to be considered before spontaneous regression is accepted. Although spontaneous disappearance of carcinoma in situ lesions after pregnancy has been described (2,3), the persistence of a considerable number of such lesions after pregnancy has been reported (1,4,5). Conversely, there is no evidence to suggest that a carcinoma in situ lesion may become less differentiated during pregnancy. It is strongly suggested that if a diagnosis of carcinoma in situ during pregnancy is made on the basis of cytologic and histopathologic changes, which according to past experience are known to have progressed to invasive carcinoma, a regresson of the lesion should not be encountered following pregnancy. It is therefore my opinion that cervical lesions during pregnancy behave in the same manner as in the non-pregnant woman, if the differential diagnosis between epithelial dysplasia and carcinoma in situ is made according to well-defined criteria for cytologic as well as histologic specimens.

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EDMUND SCHÜLLER

Vienna, Austria

Out of 1007 cases of surgically treated cervical carcinomas, the author observed a total of 21 pregnancies. All of the pregnancies, which had not been treated before the last trimester, had relapses and died, at the latest, two years postoperatively, although several of them had been treated during Stage I of the disease.

Of a group of 24 pregnancies with cervical carcinoma at the Mayo Clinic assessed by Malino, et. al., none of the patients who were more than seven months pregnant at the commencement of treatment could be permanently cured. Fistner, et. al., who observed 136 cases of cervical carcinoma in women pregnant when treatment was started, emphasized the fact that the results of treatment in the last trimester were very poor.

In contradiction of many authors, such as Weibl and Stockl, who do not see a completely poor prognosis in the combination of pregnancy and carcinoma of the cervix, the observations given above lead to the conclusion that advanced pregnancy is a most menacing complication in carcinoma of the cervix. Only when the cervical carcinoma is detected and treated during the first and second trimesters of pregnancy, is the prognosis apparently as good as in the case of non-pregnancy. The reason for the rapid dissemination of carcinoma during advanced pregnancy could be the loosening of tissues and the widening of lymphatic spaces.

Therefore, it is advisable to examine, by means of colposcopy if possible, the cervix of any pregnant woman in the early and middle third of pregnancy, and to take a smear for cytological examination.

If the results are positive, a histological examination must follow. This is most suitably done using the material obtained from a cone biopsy. In our experience, this minor operation does not necessarily result in the loss of the fetus.

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DISCUSSION

A. J. BRET and F. COUPEZ, Paris, France:

We have not had sufficient experience with the question of prognosis of invasive cervical carcinoma in pregnant women, but we are greatly interested in the statistics of Bickenbach and Soost and are in full agreement with their therapeutic conclusions.

The really delicate question seems to be the prognosis of carcinoma in situ during pregnancy and in this respect the figures of Dalian, Simatos and Nuovo and their conclusions are of great interest.

Our opinion is as follows:

1. Too many lesions were and are still classified as carcinoma in situ. In this respect Nieburgs is correct when he demands uniformity in histological terminology.

2. The histological misinterpretation of lesions (which later showed regression) seems to have induced an erroneous conclusion about the prognosis of the true carcinoma in situ. Undoubtedly the true carcinoma in situ detected during pregnancy is the same lesion as the carcinoma in situ detected in other periods of life. It is only a question of distinguishing certain very suspicious dysplasias, in which regression is still possible, from carcinoma in situ.

Due to our own experience with irregular dysplasias which still showed regression, we are convinced that pregnancy is an indisputable factor in the aggravation of the potential of a lesion to become malignant. As a consequence of this we believe that rapid treatment is indicated after a period of observation which should not exceed six months.

ALFRED GLÜCKSMANN, Cambridge, England, U.K.:

There is general agreement that the prognosis for cancer of the cervix is the same in the early trimesters of pregnancy as in those patients who are not pregnant. This observation may serve as an indication that in these cases the two phenomena (pregnancy and carcinogenesis) merely coincide but do not interfere with each other. For the last trimester and for postpartum cases the results are generally bad. In our material which comprises mainly postpartum cases, the distribution of histological types of tumors differs from that in non-pregnant cases (see table on page 2). For any given tumor type and clinical stage, the prognosis is the same for pregnant and non-pregnant patients, but in cases associated with pregnancy the incidence of refractory tumor types such as the "mixed cancers" is far greater than in non-pregnant women. In these cases the prognosis is bad (see table on page 2), and for this group we suggest that endocrine changes in pregnancy influence the tumor type and with it the curability.

I should like to ask Dr. Dalian and co-workers whether or not a comparison of the pregnant women with the non-pregnant of the same age-group shows the same trends as she has described. The low incidence of invasive cancer in pregnant women may be related to their lower age as compared with non-pregnant patients. On the other hand, one might expect a higher incidence of carcinoma in situ in the younger, pregnant women and this may be obscured by combining all age-groups in the class of non-pregnant patients.

PETER STOLL, Heidelberg, Germany:

In this very comprehensive study the number of invasive carcinomas of the cervix is compared in pregnant and non-pregnant women. The authors find invasive carcinoma five times more frequent in non-pregnant than in pregnant women. For this comparison we have to take into consideration that in the group of non-pregnant women with cervical carcinoma there are a large number past the child-bearing age. I feel that it would be worthwhile to compare only women of the same age group; therefore, take only non-pregnant women between 18 and 44 years and compare these with the pregnant patients.

CLOSING REMARKS

EDMUND SCHÜLLER:

As stated by all authors the poor prognosis of cervical carcinoma in the last trimester of pregnancy and also post partum presumably is due to the loosening of cervical tissue during pregnancy and not to the direct influence of endocrines on the tumor itself. Cervical tissue, loosened because of pregnancy, will resist the destruction of cancer much less than the cervical tissue of non-pregnant women.

As Glücksmann says, the rareness of the coincidence of pregnancy and cervical carcinoma is due to the low age of pregnant women as compared with non-pregnant women. As far as carcinoma in situ is concerned, I could not detect any higher incidence in the material from pregnant patients which I examined.

HERBERT E. NIEBURGS:

A greater incidence of refractory tumor types such as the 'mixed cancers' in pregnant women and their possible relationship with the hormonal state during pregnancy is a very important point brought out by Glücksmann. It is regrettable that space does not permit dwelling upon the interesting aspects of the morphogenesis of cervical carcinoma in relation to hormonal function.

Stoll's suggestion to compare the prevalence of invasive carcinoma in pregnant women in the same age group as the non-pregnant women is a very excellent one and the only valid statistical approach. I would like to add that, instead of comparing an age group between 18-44, the comparison be made for each decade.

VIOLETTE M. NUOVO:

The remarks of Glücksmann and Stoll about our study are most interesting. We are giving a picture of the incidence of carcinoma in situ and invasive carcinoma in pregnant and non-pregnant women compared to the age when the diagnosis was made (Fig. 1).

The percentage of invasive carcinoma in 20 to 36 year old pregnant women seems more than in non-pregnant women of the same age, with the highest percentage around the age of 30. This can be due to the fact that most women, having their children mainly between the ages of 20 and 35 or 40, have frequent gynecological check-ups during pregnancies, at which time cancer can be revealed. On the other hand, non-pregnant women unfortunately do not usually request a gynecological examination if they have no abnormal symptoms. This could explain:

1. that even if some of these patients had an asymptomatic cancer before pregnancy the diagnosis might only be made during a pregnancy.

2. that the highest percentage of invasive carcinoma in pregnant women is at the age of 30 while in non-pregnant women it is at the age of 45. These latter ones might wait until they have abnormal symptoms before seeing their gynecologist. (Under such circumstances, cancer diagnosis might be done at a more advanced stage; this could explain the fact that in our records the only instances of death occurred in the non-pregnant women, and the percentage of recurrence is much higher among non-pregnant women.)

We are afraid we cannot answer Stoll with all the accuracy we would have wished since we had the age list for all women with cancer, but we did not have time to make an age list for all the women with negative findings who were included in our study.

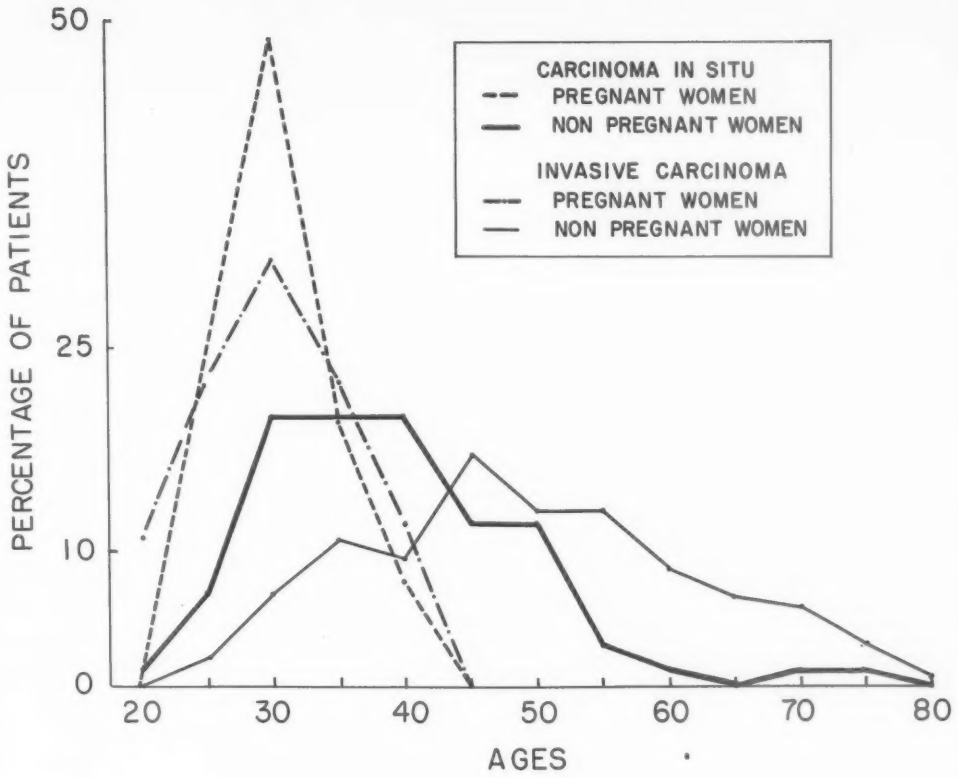

Fig. 1. (Violette M. Nuovo)

HISTOMORPHOLOGY OF CERVICAL CARCINOMA DURING PREGNANCY

FRIEDRICH BAJARDI
Graz, Austria

During the last 10 years (1948 through 1957) 13 cases of grossly invasive cancer of the uterine cervix during pregnancy were observed at the University Department of Gynecology and Obstetrics in Graz. Histological re-examination was possible in ten of these cases in which the material for investigation (sections and most of the tissue blocks) was still available.

These ten averaged 35.3 years of age, the youngest being 23 and the oldest 44. On the average they had been pregnant 6.8 times and they had had 4.3 deliveries.

In six cases the tumor of the cervix was proved histologically as a predominantly undifferentiated squamous carcinoma, while showing poor or fair differentiation in a few places. In two other cases, which at first also showed squamous carcinoma with fair differentiation in certain places, we found some sporadic columnar components (glandular formations) by means of special stainings. In another case the tumor was mainly composed of strands of small cells of the signet-ring type, containing mucoid material. Only in very few other places of this tumor were columnar cells predominant. The last case showed a different type, an anaplastic carcinoma with most of the cancer cells columnar in shape with very polymorphous nuclei and often containing prominent nucleoli. The cancer cells at the periphery of the strands have individual nuclei which tend to be eccentrically placed toward the center of the strand. Their cytoplasm appears glassy. At the center of the strands the cells showed sporadic parakeratosis.

It was Glücksmann, who, during my recent visit to Cambridge, drew my attention to these "mixed carcinomas," which have been described by Glücksmann and Cherry(1). It is striking that there were four mixed carcinomas among our ten cases of carcinoma during pregnancy. In the large quantity of material of Glücksmann(2) the portion of mixed carcinomas among the pregnancy cases was 51%, although they represented only 8% of the total number of carcinomas of the cervix.

The author's investigations, as to the manner of tumor growth during pregnancy, showed a preponderance of invasion on a wide front (six cases). Only in two cases was a marked dissociation of the strands of the cancer seen. In the remaining two cases the manner of growth could not be ascertained.

There was, except in three cases, a marked inflammation of the stroma demarcating the tumor, whereas in three other cases this cellular infiltration was very poor and even missing in another case. The three remaining cases did not allow a determination of the infection. Consequently these results agree to some extent with those of Stoll and Riehm(3). Whether or not the absence of marked inflammations is significant for pregnancy cannot be decided by means of a small number of cases. As a matter of fact, we found carcinomas without demarcating infection also in non-pregnant women.

Besides this, we could observe in our cases the typical pregnancy changes of the cervix (4,5,6,7,8): edema of the stroma, decidual formations (two cases only), enlarged and congested vessels and proliferation of the epithelial tissue. All of the cervical glands that were found in the sections (eight cases) were hyperplastic.

There is also a practical value in this latter statement. The finding of particularly large formations of cancer in the stroma usually means a grossly invasive carcinoma. During pregnancy, however, the possibility must be taken into consideration that these pictures represent hyperplastic cervical glands taken up by a carcinoma in situ.

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JEAN A. de BRUX AND JACQUELINE DUPRÉ-FROMENT
Paris, France

According to certain authors (Varangot, Violette Nuovo and Vassy, Carrow and Greene, Greene and Peckham), pregnancy favors the appearance of cancer of the cervix. The statistics published by various schools of theory seem to furnish arguments for extremely contradictory hypotheses. These contradictions result essentially from the fact that there exists no criteria enabling us to determine whether a given lesion resembling a carcinoma is likely to regress (and hence is not a true cancer), or whether, on the contrary, it is likely to invade the tissues and metastasize.

The experiments of Mullen and Foraker are now to classic to be reviewed here, save to observe that they emphasize the absence of criteria by which all pathologists may distinguish certain dysplasias of irregular cellular structure and architecture from a carcinoma in situ. As the situation now stands, certain pathologists base their opinion on nuclear anomalies, others on the more or less numerous and more or less atypical mitoses, others, again, on the architectural characters.

Now, pregnancy profoundly deranges the architectural and cellular norms to which we are accustomed, - thus, the frequent errors of interpretation leading to false diagnoses and irreparable interventions.

Our present purpose, therefore, is not to describe the carcinoma which is already invasive, differing in no respect from the usual epidermoid cancer but which gravidity whips into activity, but rather to study systematically the cervical anomalies related to pregnancy, and especially, to attempt a discrimination between certain very abnormal dysplasias, "carcinoma in situ-like," and the true carcinoma in situ. This intention may appear daring; but the ten cases which we have been able to follow and observe during pregnancy, with biopsies and smears and under colposcopic control (thanks to our colleagues Bret and Coupez), and with serial sections of amputations and conizations of the cervix, have now given us the means of forming a very different interpretation of the histological and cytological pictures.

NORMAL SQUAMOUS EPITHELIUM DURING PREGNANCY

During normal pregnancy the squamous epithelium is roughly composed of only two varieties of elements: the layers of the internal and external basal cells, and the layer of intermediate cells. Maturation (rather incomplete), moreover, involves only the nucleus. This character, added to the larger than usual nuclear volume of the germinal layer, offers a partial explanation of the formation of navicular cells.

The cells of the basal layer have an active, florid aspect, with nuclei voluminous but perfectly round, and whose active chromatin is minutely punctuated, regular but accentuated.

As maturation of these voluminous nuclei is imperfect in the upper layers, there is noted a transverse retraction, with one or two folds, and a granular condensation of the chromatin, as appears in the navicular cell.

The essential character, therefore, is a defect in the normal evolution toward cellular maturation; the nucleus makes a timid start that ends only in its very incomplete retraction.

The dyskaryotic elements

This character is more readily visible when the elements arriving at the surface of the epithelium are very voluminous from the start. In fact, in the hyperactive basal layers, there are frequently observed elements whose nuclei are "obese." They are very large but are otherwise without anomaly; they are finely reticular, without prominent nucleoli, and the nuclear membrane is fine and regular (Fig. 1). The retraction of this variety of nuclei occurs in the very same way as that of the normal cells and gives rise to cells whose nuclei, only slightly retracted, will be bi- or trilobed, somewhat irregular, with facets and chromatin folds (which are never very marked and whose aspect corresponds to the classic images of so-called "dyskaryosis of pregnancy") (Fig. 2). In these cases there can fre-

quently be noted a thin, unicellular layer of elongated elements whose cytoplasm shows a tendency toward slight cornification, whereas the nuclei remain voluminous. (There are eosinophilic cells but with large nuclei that may be mistaken for pyknotic and eosinophilic cells.) (Fig. 3.)

Fig. 1

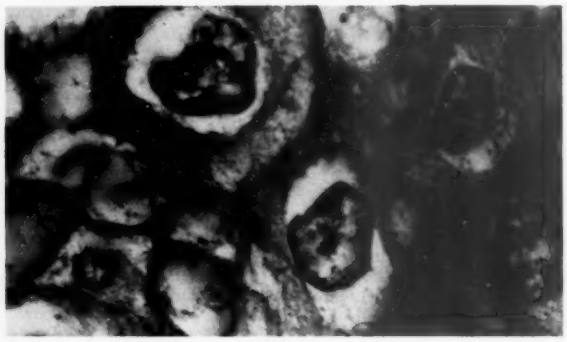

Fig. 2

Fig. 3

METAPLASTIC EPITHELIUM AND THE DYSPLASIAS

If the ectocervical squamous epithelium shows hyperactivity, sometimes with a harmonious super-abundance of elements, the columnar epithelium like-wise reflects this hyperplasia, which at first involves the reserve cells situated at the base of each columnar element. The future of these replacement cells is modified: they multiply, become hyperplastic, and will determine the very frequent phenomenon of indirect metaplasia. The new layer of germinal cells will give rise to a squamous epithelium whose aspect will range from discreet paranormal activity to severe hyperactivity.

The frequency of ectropions during pregnancy and the various endocrine effects greatly increase the frequency of the phenomenon of squamous metaplasia. The hormonal disequilibria (of placental, suprarenal or hypophyseal origin) are the source of cellular and architectural atypia which we shall attempt to classify.

A. The regular dysplasias during pregnancy

These are frequent. There is noted a marked hyperactivity of the basal layers, whose cells appear neatly piled, with very chromatic nuclei, and prominent nucleoli testifying to an activity further exteriorized by the presence of numerous mitotic figures. Here and there is found a cell more voluminous, with a large nucleus, rather dense but regular. This is nothing more than a simple exaggeration of a normal pheonomenon of pregnancy. The atypia occurring during the course of maturation of the elements constituting the epithelium will condition the aspects of this dysplasia (Fig. 4).

It is true that the cellular architecture remains normal, but modifications will appear in the maturation of these elements. Voluminous at first, the nuclei present a beginning of retraction as they

rise in the epithelium; this retraction is never sufficiently marked to reach pyknosis. The nuclei remain voluminous, with chromatin folds, or sometimes densification. Certain elements remain enormous even in their attempt at retraction.

The cytoplasm likewise is modified, but, contrary to what is seen in normal pregnancy, it tends to become cornified. Towards the upper one-half of one-third of the epithelium, the cytoplasm enlarges and becomes polychromatophilic, sometimes even distinctly eosinophilic. The polygonal cells are mutually contiguous and in the most favorable cases show intercellular bridges.

In the superficial part the elements become elongated and flattened. At this level the retarded nuclear retraction occurs rather abruptly, leaving a pale halo in the cytoplasm (Fig. 5).

Examination under low magnification is striking for the discrepancy in maturation of the ratio of cytoplasm to nucleus. The nuclei remain large, hyperactive, sometimes multilobular, and chromatic, with transverse folds of retraction, in a cytoplasm which tends toward cornification or which is already cornified. The mitoses, moreover, are rather high in the cellular layers. These facts cast an element of suspicion on regenerative lesions which would be banal if there were not the interference of the cytostimulative factors of pregnancy. It should be noted that the architecture often remains normal, and that only the nuclei remain florid, with only a slight retraction, sufficient to give them an atypical character (Fig. 6).

The perception of these facts of basal cellular hyperactivity during metaplastic pheonomena, added to the discrepancy in cytoplasmic and nuclear maturation, will permit a better understanding both of the irregular dysplasias and of the aspects of carcinoma in situ.

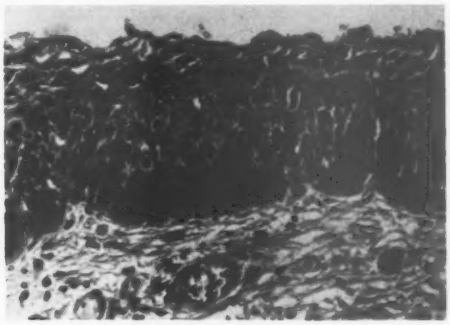

Fig. 5

Fig. 4

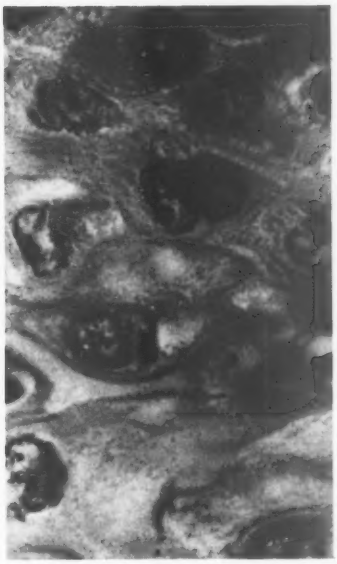

Fig. 6

B. The irregular dysplasias

Their character of gravity will depend:

(1) on the height to which the basal layers with hyperactive elements rise in the epithelium and

(2) on the aspects of maturation of these elements.

Thus, there may be found cellular elements of the basal type occupying one-half or more of the height of the epithelium. They are immature, with bi- or trilobular nuclei and dense, irregular and granular chromatin; they are elongated perpendicularly to the basal membrane and crowded against each other.

Rather abruptly, there appears a change in these elements. Their cytoplasm seems to widen and spread, the longitudional axis is no longer perpendicular to the basal membrane, and one notes an architectural atypia of impressive appearance (Fig. 7).

In addition, there appear phenomena of maturation involving the cytoplasm and the nuclei, which, in the case of the latter, show a marked irregularity. Certain nuclei are suddenly retracted, and their condensed and shrunken chromatin forms an irregular mass. Others, on the contrary, present a bi-or trilobular aspect, with irregularities, facets, folds, zones of intranuclear pseudo-vacuolization, and densification of the nuclear membrane (Fig. 8).

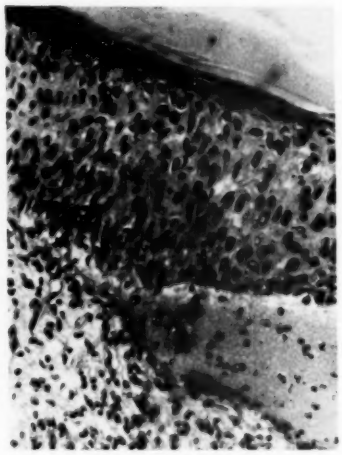

Fig. 7

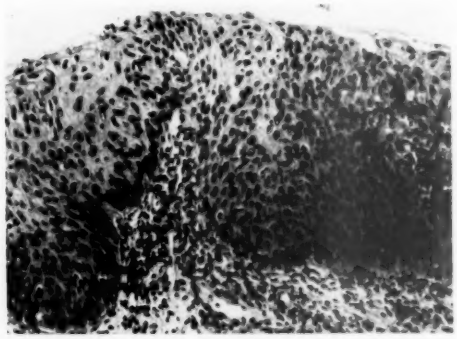

Fig. 8

A priori, the architectural and nuclear polymorphism is so startling that it evokes the hypothesis of carcinoma.

It is the degree of cytoplasmic maturation that will be the valid test of such a lesion. The cytoplasmic contours should be sought with great care. These will sometimes be found, very distinct, even with intercellular bridges, more or less well-outlined but real. Thus, there are found zones of atypical architectural and cellular morphology, but whose cells present connecting bridges, side by side with identical zones in which there are no intercellular links.

Finally, at the surface there may be seen layers of markedly elongated cells parallel to the surface and exfoliating in the form of flattened, cornified, fibroid elements (spindle-cells), with chromatic and elongated nuclei.

Hence, the cytoplasmic maturation, at least in pregnancy, seems to us much more important than the nuclear maturation, for the gravidity prevents the pyknosis of elements which at the start are very hyperactive.

CARCINOMA IN SITU AND "CARCINOMA IN SITU-LIKE"

We apologize for this nomenclature, which is our own, and which we shall now attempt to explain:

In certain cases, the cells of the basal layers are present as high as the upper one-third of the epithelium and even higher, without a beginning of nuclear retraction; then, abruptly and without transition, the cells lose their orientation perpendicular to the basal membrane and lie parallel to the surface (Fig. 9 and 10).

Fig. 9

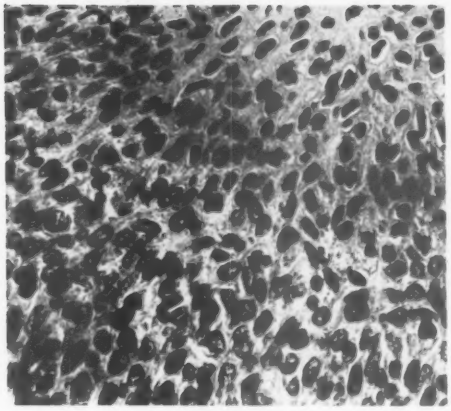

Fig. 10

The cells of such a lesion show quite special characters. Their distribution is very polymorphous, and their surface often variable. One fact, however, dominates the cellular morphology: the disparity of the nuclear and cytoplasmic aspects. Whereas the cytoplasm becomes eosinophilic (hence tending toward cornification), the nuclei remain very voluminous, with the chromatin containing large irregularly distributed granules, a thick nuclear membrane, and a striking scarcity of nucleoli. On the other hand, there is also noted a striking multitude of mitoses, presenting anomalies so exceptional, and with the very large chromosomes being so irregularly distributed, that this may be taken for karyorrhexis. This abundance of anomalies, nuclear and especially mitotic, generally elicits the diagnosis of carcinoma in situ (Figs. 11, 12).

But it should be remembered that in the pregnant woman the classical images are very often false.

In our opinion, two aspects so opposed as:

(a) the very marked tendency toward cytoplasmic maturity, and
(b) the tremendous nuclear anomalies and the startlingly atypical mitoses,

are not the expression of malignancy, but of the dysfunction of hyperactive cells, and, coupled with superficial differentiation, indicate the possibility of a regressive lesion, which we shall call "carcinoma in situ-like."

The cytoplasmic maturation of the elements of such a lesion generally attracts little attention, the pathologist lending more importance to the anomalies and atypical mitoses of the nuclei. But it should be remembered that mitoses and nuclear anomalies are often only a sign of cellular dysfunction (cf., necrosed or irradiated tumors). It is therefore probable that such anomalies are often produced by a decrease in the distribution of oxygen. Furthermore, with the exception of the mitotic anomalies,

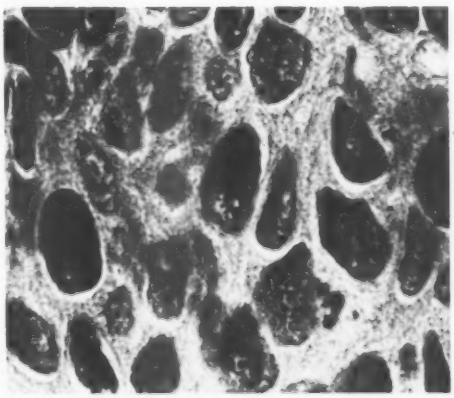

Fig. 11

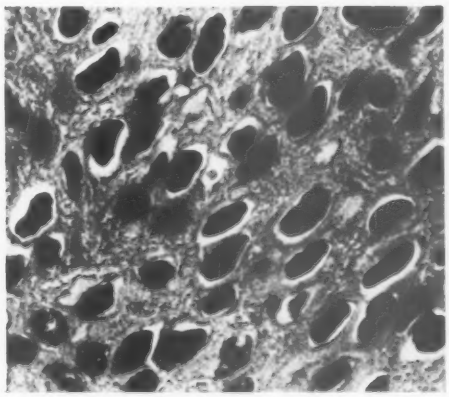

Fig. 12

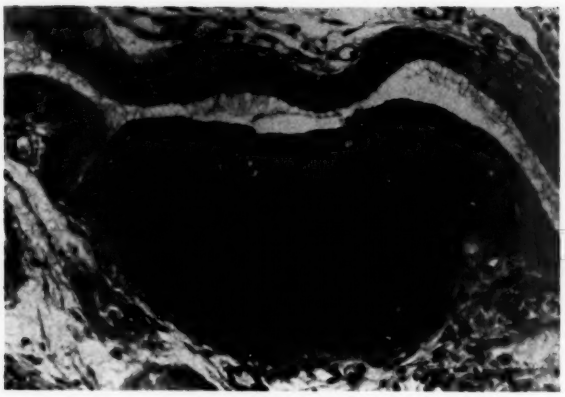

Fig. 13

the cellular morphology and the architecture are identical to those of the irregular dysplasias; the coexistence of the two aspects may even be noted on the same slide.

The true carcinoma in situ, which has no tendency to regress, even long after accouchement, presents an impressively monomorphous aspect. The cells are all of the same type, from the basal membrane up to the surface. Vertically elongated and lined up one against the other in "parade-form," they show a slender ring of pale cytoplasm surrounding a nucleus whose chromatin is very dense and black. If the mitoses are rare, the amitoses, on the contrary, are frequent. This nuclear monomorphism, the amitoses, while less spectacular than the mitoses of the preceeding form, and the total absence of cytoplasmic eosinophilia, indicate indisputably the malignant character of such a lesion (Fig. 13); however, the last upper layer exfoliates with cytoplasmic eosinophilia and discrete nuclear retraction.

But these forms of true carcinoma in situ are rare. We may state, having followed two such cases (a third case is still under question), that cervical conization several months after parturition showed neither regression nor invasion.

CONCLUSION

A cervical lesion occurring during pregnancy may be considered a true carcinoma in situ only if:

> the cells retain their immature character until exfoliation; there is not even an "attempt" at cytoplasmic cornification; the nuclei are dense, voluminous and chromatic and divide principally by amitoses.

The other lesions, however striking they may be, regress after parturition.

JORGE CAMPOS R. de C.
Lima, Peru

We present our histological observations in ten cases of cancer of the cervix associated with pregnancy (eight uterine and two tubal), found in a series of 1,762 cases of cancer of the cervix studied between June, 1952 and May, 1956.

All of them correspond to infiltrating squamous carcinoma; their histological characteristics do not differ substantially from cervical cancer not associated with pregnancy. In other words, cancer of the cervix in pregnant women does not seem to have any special characteristics which allow the pathologist to make such a diagnosis by only studying a biopsy on the cervix, unless he finds in the same slide decidual changes of the stroma.

However, in our cases we found a great predominance of undifferentiated types of cervical carcinoma. Well-differentiated histological types were rare. In seven cases the neoplastic tissue was formed by immature cells with hyperchromatic nuclei which predominated over the cytoplasm. Large, atypical, bizarre nuclei were frequent; cytoplasm was vacuolated, basophilic and succulent. In the stroma we observed alterations described in pregnancy, that is, edema and congestion. The neoplastic tissue was arranged in wide zones with loose cells or with weak adherences. It appears that in pregnancy

the cervical carcinoma has histological characteristics which correspond to a high degree of malignancy and to a fast growing capacity.

In four of our cases a caesarean section was performed followed by radical hysterectomy with lymph node dissection. In these cases we obtained enough material to study other cervical zones not involved by the tumor. We appreciated the existence of hyperplastic changes in the glandular and surface epithelium, such as have been described in pregnancy (1).

In four cases we could study new biopsies taken from three to eighteen months after delivery, due to the recurrence of the tumor. It was possible to compare the histological structure of the same tumor during pregnancy and afterwards. It was evident in all of these cases that the neoplasia suffered changes in its structure towards higher cellular differentiation. The neoplastic tissue became compact with more adherences between cells, with less tendency to grow loosely in the stroma; the edema decreased and the atypical bizarre nuclei were less evident. However, we could not observe, in any pregnant women, a very undifferentiated carcinoma changing after delivery to a well-differentiated form with keratinization and pearl formations.

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ROGER VOKAER

Brussels, Belgium

The Müllerian origin of the cervical squamous epithelium easily explains the phenomenon of hyperactivity regularly observed during pregnancy. These morphological changes which are so frequent during pregnancy are not specific, however. Sometimes they are so marked that it becomes quite impossible to distinguish if a lesion will regress and ultimately disappear or if it is an incipient (intra-epithelial) carcinoma.

Intra-epithelial carcinoma is usually considered (as far as non-pregnant women are concerned) the earliest malignant change. During pregnancy, however, the pathologist hesitates in calling quite identical lesions "malignant." For most authors the term cancer means bad prognosis. "Cancer" means evolutive disease and is definitely fatal if not treated. It may not be said that a lesion, the microscopic pattern of which was that of a neoplasm, was not a "cancer" just beeause later it spontaneously regressed. We shall not discuss here the question of whether or not the intra-epithelial carcinoma is, in pregnant women, a "real" or a "false" cancer. We shall ask ourselves whether or not these neoplastic lesions, once they are established, always progress and finally become invasive cancers and whether or not they may be completely cured.

It is likely that certain cervices are predisposed to carcinoma in situ. The adherents of the viral origin of cancer willingly admit that ectocervical cells react momentarily under the influence of hormonal stimuli with hyperactivity pheonomena and will assume a "quiet" pattern when pregnancy is over. The lesion does not automatically regress in every case, however. There are three possible evolutions:

(a) the lesion will become invasive.
(b) it will regress but malignant potentiality will remain in a few cells.
(c) it will entirely disappear and constitute no danger at all for the future.

The morphological pattern and criteria of diagnosis we have, do not allow us to choose among these three paths.

We believe with Epperson (1), Nesbitt and Hellman (2), Hirst and Brown (3), Johnson and Weinfurtner (4), Hahn (5), Brown and Jernigan (6), and many others, that in almost every case the lesion completely disappears when pregnancy is over, without any treatment being applied. On the contrary, Greene and Peckham (7), Carrow and Greene (8), and others have observed persistence of the carcinomatous lesion during the postpartum period.

Finally, Hamperl and co-workers (9) and Campos and Soihet (10) are not so categorical. They admit that such lesions regress but then insist that it is quite possible that a certain number of them will become invasive cancers. We believe that during pregnancy intra-epithelial carcinomas frequently appear, many of which completely regress. These crevices must be very carefully investigated and considered as possessing a certain disposition to malignancy.

Regression of carcinoma in situ is not only observed in those which occur during pregnancy, but also in the non-pregnant woman. Statistics show a far greater number of intra-epithelial than invasive carcinomas. Therefore, it is logical to admit that such lesions may regress. The prognosis of intra-epithelial carcinoma varies, of course, as to whether or not the woman is pregnant.

Thus, it appears that the only correct attitude during pregnancy is to wait. Such cases must be very carefully examined (by means of colposcopy, cytology and histology) even when the malignant pro-

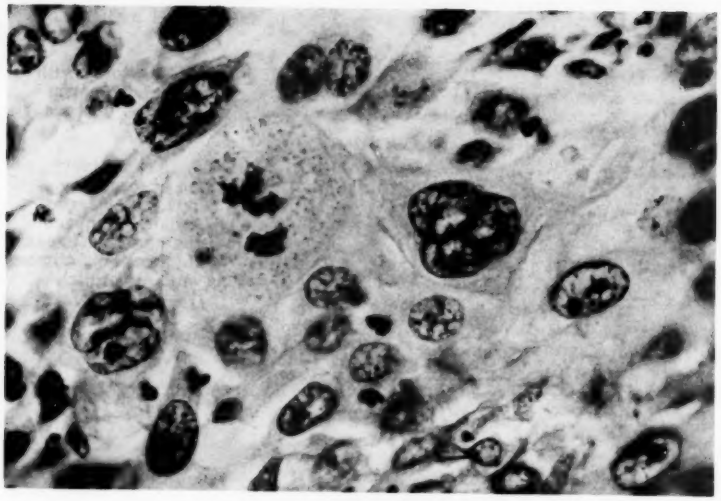

Fig. 1

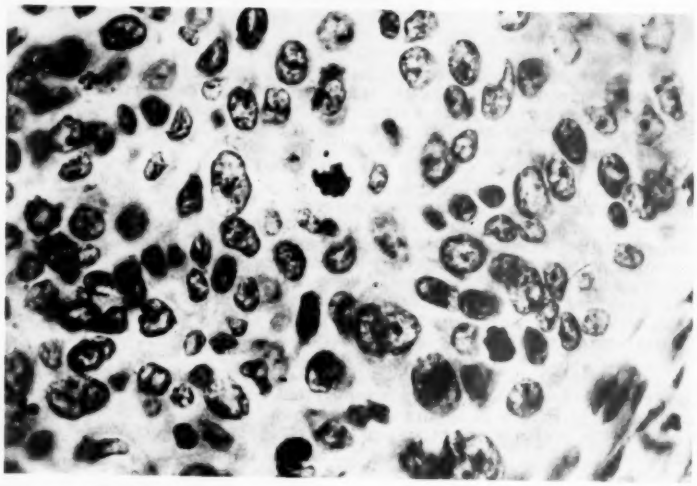

Fig. 2

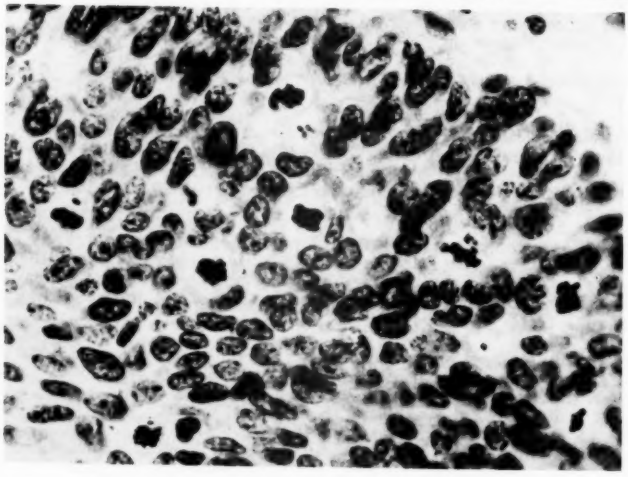

Fig. 3

liferations seem to have completely disappeared. If the lesion is still present after pregnancy, nothing should be done during the postpartum period.

We do not agree with Varangot and co-workers (11) whose therapeutic procedures do not vary whether the woman is pregnant or not. These authors, state that no lesion was found in the surgical specimens in several cases, when cytology and initial biopsy were positive. Novak and Galvin (12) also describe cases where it has not been possible to diagnose carcinoma in situ by histological examination of the surgically removed uterus. We do not agree either with Hamperl and co-workers (9). Since carcinoma in situ was far more frequent than invasive cancer in pregnant women, the latter authors (9) consider both lesions quite different entities. In my opinion there is no doubt that the way varies in which these lesions evolve. This does not mean, however, that these nosological entities are not identical.

Invasive Cancer:

As for invasive carcinoma, some microscopic aspects (Fig. 1) are quite easy to diagnose and are absolutely characteristic of this entity, as they can never be found in intra-epithelial lesions. On the other hand, certain patterns of invasive carcinoma (Fig. 2) and intra-epithelial carcinoma (Fig. 3) cannot be distinguished from each other. However, the first picture (Fig. 2) is a deeply invasive tumor which killed the patient in a few months, and the other one (Fig. 3) is a lesion which completely disappeared after delivery. Thus, it is often very difficult for the pathologist to discern what constitutes a danger for the patient's life from those lesions which are nothing more than a predisposition to be further investigated.

It seems indispensable to make oneself familiar with these atypical patterns of the pregnant cervix as much as possible and to gather a great number of clinical and histological documents. Many biopsies should be done during pregnancy and in the postpartum period. Without going so far as to perform systematical biopsies on the cervix as Kaufmann (9) did, we think that every abnormal aspect on colposcopic examination should be histologically examined.

Clinicians should get together with a certain number of experienced pathologists to exchange opinions and to standardize the criteria of microscopic diagnosis.

I believe every gynecologist and obstetrician should make a habit of looking at the cervix of every pregnant woman, of doing a Schiller test and a colposcopic examination and a biopsy, if necessary. These techniques may be considered routine as far as a few specialists are concerned; however, they are far from being currently used by the majority of physicians who see a great number of pregnant women.

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DISCUSSION

ALVAN G. FORAKER, Jacksonville, Florida, U.S.A.:

Intense interest in this topic is indicated by the fact that four speakers were invited to present their views. Opinions on this controversial subject may be divided into "conservative" and "radical." The "conservatives" (Epperson, Nesbitt, Hellman, etc., quoted by Vokaer above) believe that there is a lesion in pregnancy virtually identical morphologically with "in situ" carcinoma in the nongravid cervix, which may disappear. In discussing this problem some years ago, we listed a fourth possibility (1) in addition to the three given by Vokaer: The phenomenon may be temporary, but perhaps indicates those women whose cervices are abnormally sensitive to hormonal or other stimuli, and who under the influence of additional factors may develop intra-epithelial or invasive carcinoma subsequently. Recent literature (Greene, as quoted by Vokaer, above, Marsh and Fitzgerald) (2) has emphasized a more "radical" viewpoint, that there is a histologically identifiable intra-epithelial carcinoma during pregnancy, which will not regress, and which can be differentiated microscopically from evanescent epithelial proliferation. Our material is rather scant, but we are still swayed by a single carefully studied case (3), in which the lesion persisted during pregnancy, survived a conization, was present six months post partum, and absent in the seven month postpartum hysterectomy specimen. A panel of experts (Hellman, Hertig, Novak, Pund, Stewart) reviewed our material and shared our uncertainty. We feel ourselves unable to diagnose intra-epithelial carcinoma during pregnancy and to be sure that the lesion may not regress later. We recommend that such cases be well followed for at least six months post partum before a definite diagnosis and therapy are decided upon. Invasive carcinoma can be diagnosed during pregnancy as at other periods.

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ALFRED GLÜCKSMANN, Cambridge, England, U.K.:

The papers of Vokaer and de Brux and Dupré-Froment are concerned mainly with the definition of the histomorphology of carcinoma in situ in pregnancy, and no comment is offered beyond drawing attention to the relevant contributions of Fluhmann (1,2) and Foulds (3) (concept of tumor progression).

We agree with Campos that there is no tumor type specific for pregnancy, though immature forms predominate. Bajardi's finding of four mixed carcinomas in his ten cases indicates that the distribution of tumor types of the cervix is affected by pregnancy. We should like to amplify this statement by a table which, in addition to 65 cases reported previously, lists 79 cases collected by J.B. Graham at the Roswell Park Memorial Institute of Buffalo, New York.

The table gives the comparative rates of incidence for epidermoid cancers, adenocarcinomas, mature adenoepitheliomas and anaplastic mixed cancers. For the histological identification of the last two groups it is essential to stain for mucin and pseudomucin (for instance with the Periodic Acid-Schiff Technique). The cure rates differ widely for the different tumor types, but are similar for the same tumor type in the English and the American Centers and for pregnant and non-pregnant patients.

Cervical cancer and pregnancy may merely coincide as, for instance, in the cases with epidermoid tumors. The high incidence of the refractory mixed cancers mentioned by Bajardi and seen in the table, suggests that endocrine and systemic changes of and during pregnancy influence the type of tumor and with it the curability.

Table I

CANCER OF THE CERVIX ASSOCIATED WITH PREGNANCY

Histological Type	Number of cases		% Incidence		% 5-year cure	
	U.S.	U.K.	U.S.	U.K.	U.S.	U.K.
Epidermoid Cancer	48	26	60	40	48	38
Adenocarcinoma	6	6	8	9	50	40
Mature Adeno-epithelioma	8	11	10	17	62	67
Anaplastic mixed cancer	17	22	22	33	0	6
Totals	79	65			39	32

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EMMERICH von HAAM, Columbus, Ohio, U.S.A.:

Vokaer agrees with Epperson and others that in almost every case the lesion classified as incipient or intra-epithelial carcinoma completely disappears when pregnancy is over without any treatment being applied. He also feels that in pregnancy certain patterns of invasive carcinoma and intra-epithelial carcinoma cannot be distinguished from each other. For this reason he recommends the repeated use of biopsies during pregnancy and during the postpartum period. Campos stresses the fact that cervical carcinoma found during pregnancy has a tendency to be less differentiated, an observation with which we agree. Bajardi warns that hyperplastic cervical glands in the pregnant cervix may be replaced by carcinoma in situ and thus simulate invasive carcinoma. Dr. de Brux differentiates between regular and irregular cervical dysplasias during pregnancy and carcinoma in situ and carcinoma in situ-like lesions. He stresses the presence of cytoplasmic maturation as an important criterion in differentiating dysplasias from carcinoma in situ.

HERBERT E. NIEBURGS, New York, New York, U.S.A.:

Cervical carcinoma during pregnancy is a controversial subject. Its adequate discussion necessarily must present a difficult task, particularly within a limited space. Nevertheless, the foregoing contributions are of great interest. Possibly, another topic entitled "Histomorphology of Non-malignant Cervical Lesions During Pregnancy" could be introduced for presentation of the essence of the problem.

The incidence, developmental course and prognosis of cervical lesions during pregnancy are of great clinical significance, though divorced from the scope of the overall title which emphasized the histomorphology. I am in full agreement with Vokaer that standardization of criteria for the microscopic diagnosis of lesions is necessary, and I should like to add that this is a prerequisite for any discussion of this topic. I, therefore, confess my inability to state whether or not I agree with Bajardi and Campos. The report of Bajardi on the findings of 13 cases of invasive carcinoma during pregnancy is interesting. It would be important to have further information as to the reasons for finding no cases of carcinoma in situ.

De Brux's and Dupré-Froment's approach to the problem is very commendable. To make a statement as to which lesion should be diagnosed as "carcinoma in situ" and "carcinoma in situ-like" is difficult, and instead of a definite viewpoint, the solution of this problem must await statistical evaluation.

Based upon long term observation of untreated cervical lesions, it is my opinion that no diagnosis of carcinoma in situ should be made unless cellular atypia is present throughout the entire epithelium, including the basal layer, with a prominent loss of stratification and with no invasion. It is necessary, however, to add that such a lesion should be treated in the same manner as an invasive carcinoma. An evaluation of the significance, management and prognosis of the non-invasive lesions exhibiting a lesser degree of atypia must await the results of long-term observation studies. In this connection, it is interesting to note that the two carcinoma in situ lesions cited have remained in situ during and following pregnancy.

PETER STOLL, Heidelberg, Germany:

Only in 14 cases of carcinoma during or shortly after pregnancy, was enough material available for a very thorough comparative study. One should keep in mind that it is always essential to use the same method and time of fixation in order to compare histological findings, especially with regard to connective tissue. We preferred Susa-fixation (after Heidenhain) and staining with hematoxylin-eosin, van Gieson, Azan, Goldner-Elastica (after Volkmann with Orcein H) and silver impregnantion after Tibor-Pap.

Comparing these 14 cases with 100 cases of cervical carcinoma without pregnancy, we hesitate to come to definite conclusions, and I only can give some general impressions:

1. Also in cases of advanced infiltration of the cervical wall or advanced exophytic growth the cervical canal with the mucin-productive glands was well intact, and the mucin production itself was abundant as seen in cases of normal pregnancy. The direction of the infiltrating process was more into the mesenchymal tissue and did not spread out very far on the surface of the ecto-and endocervix. It was my impression that in the area of mucin-producing glands and in their surrounding area, in which a decidual reaction is occasionally seen, carcinomatous growth is inhibited.
2. Within the cervical wall the growing zone of the carcinoma is very well-defined without splitting of the tumor-periphery.
3. In general, the character of the tumor and its maturity seem to be unchanged. However, comparing the number of horn-cells and horn-pearl-formations, we definitely found more in cases with pregnancy. This was especially significant in tumor particles in lymphatic vessels.
4. The most important difference is found within the connective tissue. During the intact pregnancy we found the inflammatory reaction to be very poor. The connective tissue attached to the infiltrating tumor is rich in young fibroblasts and fibrocytes, and histiocytes, with building of a very distinct network of fibrils. Formation of a "basal membrane" is always seen. Contrary to this, after the end of the gestation period (postpartum phase) leukocytic infiltration is abundant, destruction of connective tissue is very marked and collagenic fibers are very few. There is destruction of the basal membrane and splitting of the carcinomatous growth.

I may say that from the histological standpoint carcinoma of the cervix combined with pregnancy should have our special attention. Hormonal factors are influencing the carcinomatous growth and the surrounding connective tissue ("Abwehrgewebe"). Further research should be done, which might enable us to find some clues in this hormonal influence, which may be of therapeutic value in the future. I would appreciate it if Glücksmann would give us more information from his very great experience in this field.

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LOUIS J. ZELDIS and DEAN L. MOYER, Los Angeles, California, U.S.A.:

Our experience with invasive cervical carcinoma during pregnancy coincides with that of Bajardi in indicating that the outstanding histological feature is the frequency of the "mixed" carcinomas so well described by Glücksmann. In the period 1954-58 we have studied nine frankly invasive carcinomas and five superficially invasive carcinomas of the cervix in pregnancy. In five of the former and two of the latter the tumor has been either (1) a mixture of poorly or fairly well-differentiated epidermoid cells with columnar elements showing varying degrees of atypical gland formation and variable mucin production or (2) predominantly poorly differentiated cells with "glassy" cytoplasm in which occasional mucicarmine-staining droplets are demonstrable. In two of the lesions of the first type, involved pelvic lymph nodes also showed a mixture of epidermoid and adenocarcinoma. In our experience these features are uncommon except in pregnancy. We have however, seen at least three examples of the poorly differentiated, "glassy" cell variety in postmenopausal women. We have also noted this type of cell in two lesions in pregnancy which did not show stromal invasion.

In the difficult problem of deciding when to make a diagnosis of intraepithelial carcinoma in the cervix of pregnancy we have been influenced by considerations similar to those described by de Brux and Dupré-Fremont. We are reluctant to make the diagnosis in the presence of evidence of differentiation, even though it be superficial and somewhat dyskeratotic. Whether or not this is a valid criterion will require long study. Relatively few cases present valid situations for follow-up, since initial accurate classification in general requires cervical conization. This procedure is in itself undoubtably destructive of the lesion in many instances.

CLOSING REMARKS

JORGE CAMPOS R. de C.:

It seems to be a general agreement in the above discussions that although cervical carcinoma during pregnancy does not have a pathognomonic histology of its own, it frequently has an unripe structure, with "mixed forms" (Glücksmann). The prognosis of such unripe histologic types is poor in comparison to highly differentiated forms. These facts could be explained by endocrinological effects during pregnancy.

Our observations coincide with these findings.

FRIEDRICH BAJARDI:

My paper has been intentionally limited to the discussion of invasive carcinoma, for the following two reasons: (1) the histomorphology of carcinoma in situ will be discussed in a later issue of this journal, and (2) the histomorphological patterns of malignant lesions which occur during pregnancy are more pronounced in the more progressed lesions than in carcinoma in situ. I refer also to the topic in the symposium entitled "Diagnostic Accuracy of Colposcopy as Compared to Cytology in the Detection of Cervical Carcinoma During Pregnancy," where I dealt with some of the questions pertaining to carcinoma in situ.

The demand of Nieburgs and Vokaer for standardization of microscopical terminology is certainly justified, and I believe that this will be taken care of in the symposium on carcinoma in situ in this journal, when histological sections will be discussed in order to achieve uniformity in terminology.

ROGER VOKAER:

It is obvious that all authors agree that standardization of the criteria for the histomorphologic diagnosis of ectocervical lesions during pregnancy is necessary.

I am very glad to notice most authors agree with me on the various characteristics that I proposed.

Although Glücksmann regrets that nothing was said on the problem of such tumor progression, it is to be noted that the subject was especially "Histomorphology of Cervical Carcinoma During Pregnancy."

All the same, the question of the future of these lesions must be talked about and we want to range ourselves, in opposition to Nieburgs, among the "conservators" such as Foraker, with whom we are in full agreement.

HISTOMORPHOLOGY OF CERVICAL DECIDUAL REACTION

JEAN A. de BRUX AND JACQUELINE DUPRÉ-FROMENT
Paris, France

The cervical deciduoses, perceived nearly ten years ago, are now currently recognized in clinical gynecology. Their various aspects have been described, as a result of the numerous histological and cytological examinations made for the purpose of studying the epithelial modifications during pregnancy, in the search for cervical cancer, until now considered as more frequent in gravid women.

With colposcopy now having rendered possible the prompt discovery of these decidual zones, clinical practice and para-clinical and biological methods have thus given the means of a precise diagnosis of this dystrophic state (which cannot be considered as a lesion) and have demonstrated its relative frequency.

Cervical deciduosis is found to have three aspects:

pseudo-tumoral form
pure decidual form
polypoid or ectropion-type form.

A. Pseudo-tumoral form

This is a rounded formation, elevating the mucosa from underneath. Microscopically, it is composed of decidual cells piled against each other, at certain zones nearly joined together. At other points they are separated by a scanty, loose stroma, whose collagen fibers are usually dissociated and stretched by edema. Glandular lumina are absent. Numerous dilated vessels are surrounded by lympho-histiocytic elements. This large sheet of cells is covered by a columnar or squamous epithelium, the latter usually thin and containing only a few layers of cells, with small ulcerations on its surface. In some cases

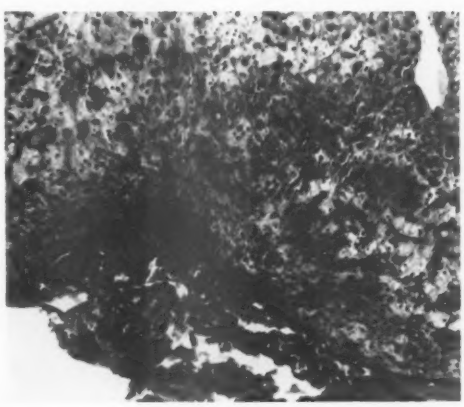

Fig. 1.

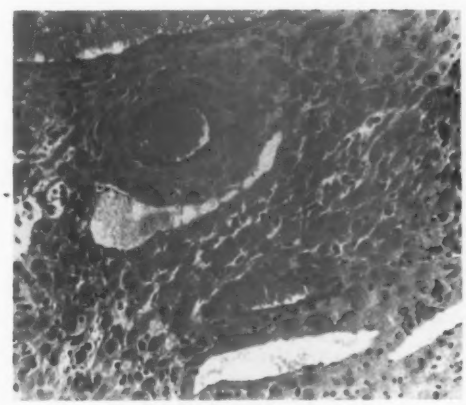

Fig. 2

the border is almost completely abraded and may be replaced by a fibrino-leukocytic exudate, so that the decidualike chorion herniates through the break thus produced in the squamous epithelium (Fig. 1).

B. Pseudo-decidual form

This variety seems to be a true fragment of decidua, in which the glandular lumina are sometimes recognizable but are compressed by the considerable hyperplasia of the chorion. This aspect is increased by the fact that the epithelial, columnar or squamous border is usually almost totally abraded. Such formations are often used as a diagnostic test for threatened abortion.

Here again there is observed a rather uniform sheet of decidual elements, arranged in dense clumps or, on the contrary, separated by a loose, edematous connective tissue. The dilated capillaries are sometimes thrombosed. Inflammatory phenomena are not infrequent, but in general are more accentuated, with some necrobiosed zones (Fig. 2).

C. Polypoid or ectropion-type form

This form is characterized by the presence of one or several groupings of decidual elements at the site of an ectropion (particularly frequent in pregnant women). In fact, this formation is composed of numerous polyadenomatous mucous glands of various forms and sizes, often sinuous, sometimes very dilated, with only very little connective tissue separating them. Crowded in among these cavities there appear patches of decidual cells; these patches may be small or sizable, often situated directly below the epithelial border at the distal part of the ectropion. The decidual transformation is found here in all its stages; sometimes this is very discrete, and the tendency toward transformation may be manifested only by a few cells grouped at one or two points. The vessels are abundant, often dilated, and their walls are thin. There is edema with hemorrhages. In this form one finds very marked inflammation, consisting of polynuclears and lympho-plasmocytes. This character is important and may in part explain the cellular anomalies which are more easily noted in this form of deciduosis.

MORPHOLOGY OF THE DECIDUAL CELL STUDIED IN SITU

In any of the histological forms considered, the decidual elements almost invariably present the same morphology:

Rather large cells (10 to 25μ), oval in form with compact cytoplasm, pink under low magnification, eccentric nuclei, rather pale and slightly violet. On higher magnification, the cytoplasm, although still compact, appears microvacuolized. The moderately small nucleus is usually found at the extremity of the long vertical axis, either touching the cellular membrane or nearer to the cytoplasmic center. The nuclear membrane is linear and delicately accentuated. The chromatin network appears as a fine, evenly-distributed peppering, with round, seamless and visible nucleoli. The cell borders are distinct and show a double outline, the inner line being slightly sinuous, the outer ring appearing denser than the rest of the cytoplasm and orange-tinged (Fig. 4). This aspect seems to correspond to a modification of the tissue texture rather than to a folding of the cell-borders, as may be more clearly observed under immersion magnification. In any case, as thus described, the decidual cell constitutes an entity which would be difficult to confuse with other elements.

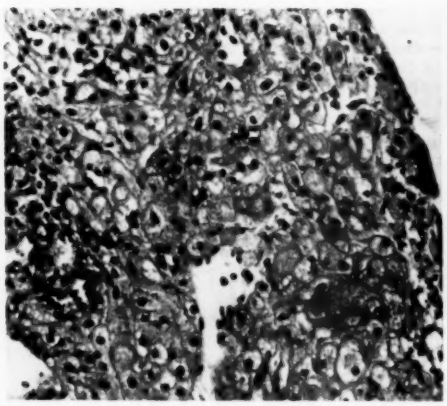

Fig. 3.

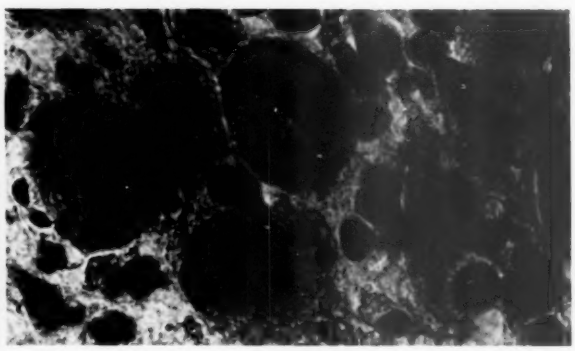

Fig. 4

ANOMALIES OF THE DECIDUAL CELL STUDIED IN SITU

Usually, the decidual elements, while following in general the previous description, may nevertheless present deviations in certain details; some are rounder, others longer and almost fusiform, others are polygonal or racquet-shaped, and some, smaller in size, have the general aspect of an internal basal cell.

The nucleus itself, usually rather small, may sometimes swell to the point of occupying a central position and the major part of the cellular volume. Mitoses are rare and seem to show signs of dysfunction.

In the pseudo-tumoral and pseudo-decidual forms the cellular anomalies are negligible, and when they exist they are banal: the cells may be binucleated or on the contrary may have a very pale nucleus undergoing lysis, with the chromatin specks fading into a pale halo. In some instances, however, the chromatin may present some modifications: either the nucleus becomes bloated and the chromatin becomes scarce (reduced to a few grainy areas in the midst of vacuolar zones), with accentuation of the nuclear membrane and prominence of the nucleolus, or the nucleus shrinks and the chromatin becomes concentrated and dense with very regular grains. At the most, the cell becomes anucleated and appears as a pink granular mass with a double outline.

Sometimes, especially in the ectropion-type form, there occurs a vacuolization of the cytoplasm which is often generalized, giving the appearance of a loose-mesh net work, limited towards the exterior by the double border, which then appears more sharply outlined. In these cases, moreover, the nucleus itself is modified, with a tendency toward pyknosis. The chromatin is dense and opaque, and the nuclear border presents some notches. Sometimes vacuolization of the cytoplasm is extremely marked, with a single vacuole present, the shrunken nucleus being pushed toward one end. However, at the periphery the double outline is still recognized.

Dysplasia of the decidual cells exists, but resides principally at the site of ectropions and polyps, apparently favored by inflammation and being even more marked when the protective epithelial border has disappeared. The cytoplasm becomes so deformed as to assume a fusiform or even fibroid aspect, rather resembling spindle cells of squamous origin, and the nucleus, appearing as if molded by the cytoplasm, is likewise elongated (Fig. 5).

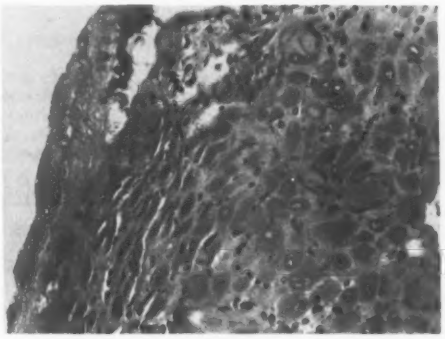

Fig. 5

MORPHOLOGICAL ANOMALIES OF THE BORDER ZONE

These identical dysplastic characteristics are again found in the epithelial border zone. In fact, it would seem that no matter what cell type is involved, it invariably reacts in the same manner when in contact with any lesion and under the influence of the hormonal context of pregnancy.

Thus, at the thinned but well-stratified squamous border, one may find badly shrunken nuclei with festooning of their borders and heterogeneous opacification of the chromatin; certain bloated nuclei remain in the superficial layers and each has a predominant nucleolus and nuclear membrane. This dyskaryosis is marked by difficult and incomplete nuclear maturation of cells, harmonious in structure, but too florid, with immature nuclei appearing all the way up to the surface.

In one of our patients we found a dislocation of the basal membrane at the level of the squamous border, with an attempt of the subjacent decidual elements to penetrate into the epithelium. The nuclei were dysplastic, and all of the cells of the lower layers showed a loose-meshed, cytoplasmic vacuolization. (Fig. 6).

When the border consists of columnar elements, the same nuclear anomalies are again recognized. In one case, however, we observed a special aspect recalling the cellular modifications of the Arias-Stella type, found at the level of the columnar elements of the endometrium after interruption of pregnancy. The cytoplasm was "blown up," vacuolar and loose-meshed, whereas the nucleus became opaque, tending toward pyknosis (Fig. 7). Comparing these elements with the subjacent decidual cells, one had the impression that the cylindrical cells, in turn, were undergoing a deciduiform transformation.

Finally, in the pseudo-decidua form, the columnar epithelium was flattened to the extreme, almost endothelioform, apparently as a result of the thrust of the enormous cellular mass it covered. As thus analysed in its smallest details, cervical deciduosis would appear easy to diagnose, at least from the histological viewpoint.

Fig. 6

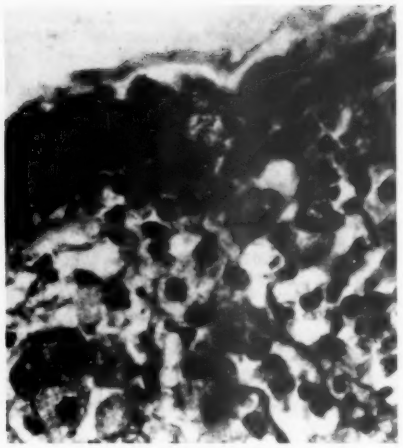

Fig. 7

COMMENTS ARE INVITED
ABOUT ANY OF THE SUBJECTS TREATED
IN THE SYMPOSIA BY CORRESPONDENCE.

THE COMMENTS WILL BE PUBLISHED
IN THE SECTION "LETTERS TO THE EDITORS."

COLPOSCOPY ON NORMAL AND ABNORMAL CERVICES DURING PREGNANCY AND THE POSTPARTUM PERIOD

JULES-ANDRÉ BRET AND F. J. COUPEZ
Paris, France

During the course of pregnancy colposcopy permits the observation of mainly four phenomena:

1. Physiological changes of the normal cervix.
2. The colposcopic characteristics of lesions which are present prior to pregnancy.
3. The appearance of new dysplastic lesions.
4. The appearance of abnormal features peculiar to the pregnant cervix and their disappearance after delivery.

A. Modifications Encountered on the Previously Normal Cervix

They are secondary to the histological alterations and include:

1. An increase in the volume of the cervix which is clearly edematous. This volume increase is mainly due to an inhibition of the stroma and increases notably from the eighth to the ninth month.
2. Modification in the color, which turns from reddish to purplish, because of hypervascularization. The vascular subepithelial network remains visible in most cases.
3. Eversion of the orificial area, the squamous border of which is becoming clearly visible. The external os itself acquires the shape of a button hole and allows the deeper parts of the cervical canal to appear.
4. The presence of a notable glare of the cervix, proving changes in the activity of the columnar glands. The color of this glare turns towards opalescence, the viscosity and resistency against wiping increases considerably.
5. The development of cylindric ectopic zones either by centrifugal progression or by ulcerations of the subepithelial hyperplastic glands.

Fig. 1. PRO, 4/23/1958, magnification 2 x, acetic acid. This field pattern was present before pregnancy and spread out to four to six times its original size between the second and the sixth month. It corresponds to a HINSELMANN II, the histological characteristics of which have exaggerated during the pregnancy without, however, reaching HINSELMANN IV. Smear: PAPANICOLAOU Class II.

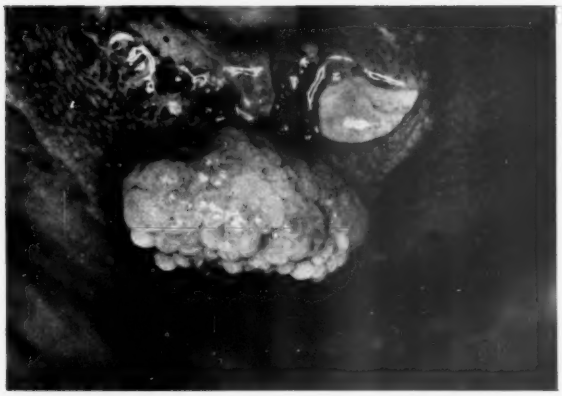

Fig. 2. ROL, 3/24/1958, magnification 1.1 x, acetic acid. Papilloma and dysplasia developed during present pregnancy. The dysplastic epithelium, periectopic field, corresponds to a HINSELMANN II to III. Smear: PAPANICOLAOU Class II.

After pregnancy a very rapid involution takes place, the cervix losing its pregnant aspect eight to ten days after delivery. After 20 to 30 days the retraction of the ectropion towards the cervical canal is completed in most cases. The residual ectopy is relatively frequent. The spontaneous process of scar formation can be extended over a long period of time.

B. Modifications Arising on Previously Abnormal Cervices

All the gynecological abnormalities can be found during pregnancy. They then take a particular shape of aggravation and instability: The ectropion pushes them out of the external os. Diffuse inflammations or vaginitis are more frequent and more extended.

1. The previously present ectopies: They increase in surface area and become more marked. The basic element, the grapelike structure of this ectopy is usually bigger with good visible vascularization. They are rarely regular sheets but are more polyploid or even condylomatoid. The superimposed infection is constant. It causes numerous hemorrhagic sheets and tissue breakdown which makes an usually easily recognizable and non-suspicious-appearing lesion unrecognizable and monstrous.

2. The areas of reserve cell proliferation: They become rare in their classic form, since the advancement of the squamous epithelium is stopped by abundance of the glandular secretion. The reserve cells usually disappear and are replaced by the ectopy. The incidence of red atypical zones is variable; we deal most often with ulceration due to inflammation.

3. The previously present zones of leukoplakia and dysplasia: They clearly display their optical characteristics, the true leukoplakias, the "grounds" and "fields," being more clearly visible. Their surface area and their thickness increases noticeably. Histologically the changes become more severe in numerous cases and these changes may temporarily or permanently bear the features of dysplasia or even carcinoma in situ. The reaction of keratosis and prekeratosis becomes more accentuated and this explains the more intense appearance.

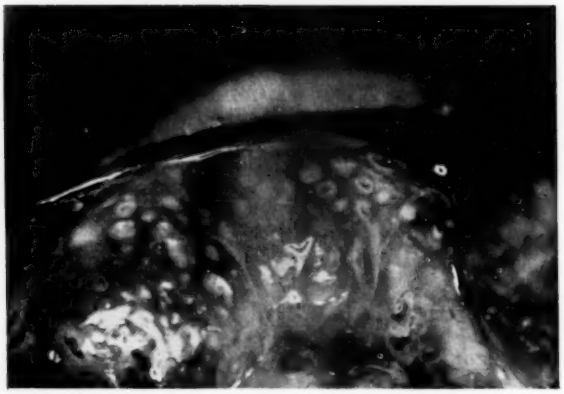

Fig. 3. RAM, 1/10/1958, magnification 1.1 x, acetic acid. Pregnancy fourth month, droplet pattern and white leukoplakic zones which developed during present pregnancy. Histology: dysplastic epithelium of the type HINSELMANN II-III and IV with glandular involvement. Six months after delivery the regression of the lesion is complete. Smear: cellular atypias PAPANICOLAOU Class III.

C. Formation of New Dysplastic Lesions

1. Formation of the usual colposcopic lesions: In a great number of cases colposcopy during pregnancy permits observation of the new formation of dysplastic zones, originating from regenerative tissue due to metaplasia. The metaplasias are common at the sites of the ectopies of pregnancy and sometimes take from their formation the aspect of leukoplakias, "ground" or "field" pattern. The newly arisen lesions develop towards two directions - either towards histological normalization and colposcopical disappearance or towards permanent regenerative dysplasias.

2. Formation of unusual colposcopical lesions, droplet pattern: During pregnancy those glands which open towards the squamous epithelium and which originate from an old, healed ectopy are often the site of squamous metaplasia. When the character of a metaplasia changes to a dysplasia, one encounters a peculiar colposcopic picture, which we have called the "droplet pattern" (image en gouttes). It reminds one of moniliasis: a spangling iodine positive epithelium with round or oval iodine negative small spots. Sometimes the orifice of the gland remains visible. The advancement of this process may disturb the borders of those spots which finally rejoin and eventually lead to the typical shape of a leukoplakia or field. The "droplet pattern" may be found outside pregnancy as well, but there it is much less characteristic. As a general rule we deal here with a transitional formation which eventually will lead to the usual forms or disappear.

D. Shapes Peculiar to Pregnancy

The decidual reactions in certain cases can become visible in the colposcope. According to the size of infiltration of the stroma and the position of the cell groups in relation to the epithelial layer one may observe:

---simple congestive epithelial bulging,
---exophytes of quite different shapes and clearly visible embossements, clearer and quite red,
---ulcerations of particular character.

The knowledge of these colposcopic features permits making a diagnosis more frequently of those lesions which were hitherto considered rare and which may well have been responsible for sometimes frightening symptoms, such as hemorrhages.

E. The Development of Colposcopic Atypias

The development of colposcopic atypias is different during and after pregnancy...

Lesions which have recently arisen can expand in their size and shape, but they never seem to disappear. A delay of four to six months after delivery is necessary to affirm either their stabilization or their definite aggravation.

Atypias formed during pregnancy are much less stable before delivery. Whatever their histological type, they can either progress or regress. The anti-inflammatory treatment seems to us to have a definite influence on their behavior. After delivery it takes at least four to six months to decide whether or not they are going to disappear or to aggravate. After delivery all the visible atypias participate in the postpartum involution. The decrease in surface area is the rule. The centripetal migration towards the external os is constant. In certain rare cases the lesion can reach the endocervical canal and escape detection on examination. In all other cases colposcopy perfectly permits the follow-up of the development of atypias, whether or not detected by cytology.

F. Conclusion

Colposcopy is of a considerable interest during pregnancy. Often it allows the detection of a superficial deciduosis. It permits following and checking histologically the development of previously present atypias, as well as observing and understanding the appearance of new atypias: dysplasia scars which are very apt to evolve later into malignancy.

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WARREN R. LANG
Philadelphia, Pennsylvania, U.S.A.

Colposcopy (binocular magnification of a well-illuminated portio) has a definite contribution to make in the evaluation of the ectocervix of pregnancy and of the postpartum period. The procedure can be performed with ease and safety. It may be difficult to visualize adequately the entire portio in multiparous patients but a perforated finger cot over a bivalve speculum aids in preventing the vaginal walls from obscuring the view. During gestation, the characteristic hyperemia and the tendency, especially of the columnar epithelium, towards hyperplasia are frequently noted (1) (Fig. 1).

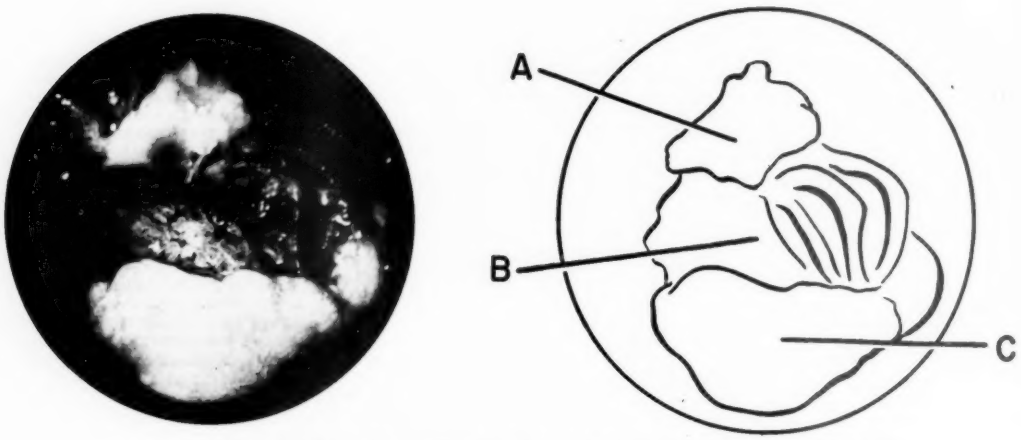

Fig. 1. Colpophotograph and accompanying diagram of portio of pregnant cervix showing a) mucous plug, b) hyperplastic columnar epithelium and c) hyperplastic squamous epithelium (histologically a papilloma).

The average cervix of pregnancy discloses a perioral, reddened area, which the clinician terms an "erosion." Because of increased vascularity and succulence with pregnancy, this lesion may even appear suspicious for malignancy to the naked eye. Colposcopically, as in the non-pregnant cervix, an "erosion" consists usually of an ectopy (columnar epithelium on the portio in the region of the external os) surrounded by elements of columnar epithelium in squamous epithelium in the form of (a) gland openings, (b) Nabothian cysts or (c) islands (Fig. 2). This zone of mixture of epithelia is known to colposcopists as the transformation zone. Histologically, epidermization is present in this area and for this reason abnormal cells may be desquamated. The transformation zone is thought to be the region in which most histologic atypisms and carcinomas arise.

With the two main vaginal infections, Trichomonas vaginalis vaginitis and Candida albicans vulvovaginitis, more or less typical gross and colposcopic findings appear. By colposcopy, trichomonal infections often disclose clusters of capillaries with or without a central necrotic area; characteristic tiny white circular areas with a red central spot may also be seen (2). With either infection, varying inflammatory changes are noted.

As would be expected, colposcopic changes suggestive of atypisms and early carcinoma may be found. Whether pregnancy increases the occurrence of atypical colposcopic patterns is as yet uncertain. As in nonpregnant women these changes may consist of the three types of leukoplakia: simple leukoplakia (area of whitening), ground leukoplakia (yellow-white area with stippled appearance), mosaic leukoplakia (yellow-white area with a mosaic pattern) (Fig. 3). Non-iodine staining areas may also be present. There may be sites of proliferation or ulceration (true erosion) in addition to abnormal vascular patterns (adaptive vascular hypertrophy of Hinselmann) (3). An abnormal transformation zone may be significant; this demonstrates a yellow, glassy appearance with friability, and possibly increased leukoplakic changes around gland openings. The more marked the abnormal findings are, both qualitatively and quantitatively, the more likely it is that malignancy is present.

In our experience from colposcopic examinations of the immediate postpartum cervix (4), the relative lack of damage to the portio from spontaneous delivery is quite surprising. This is in opposition to the currently accepted theory of benign cervical "erosion" - namely, that there is loss of squamous epithelium followed by columnar growth from the canal and then a growth of squamous epithelium toward the os. Colposcopically, the minute areas of actual erosion heal from the base to the surface, primarily with squamous epithelium. Lacerations and anterior lip bruising are also found immediately after delivery.

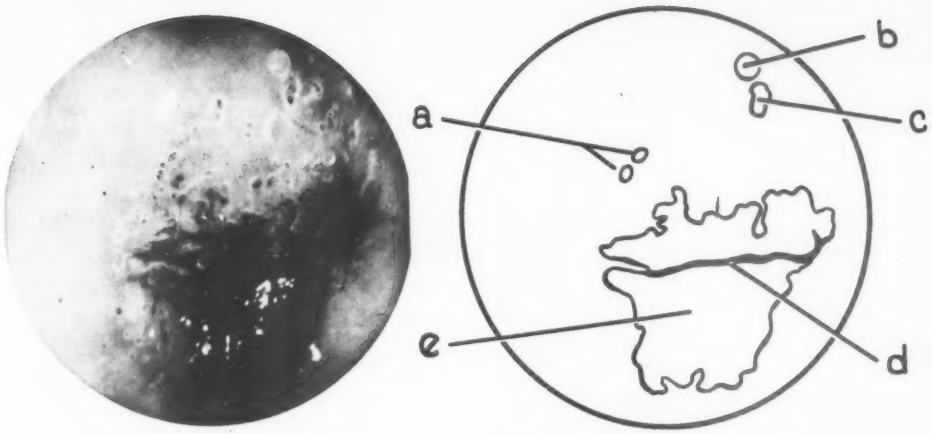

Fig. 2. Colpophotograph and accompanying diagram of so-called "erosion" of pregnancy showing (a) gland openings, (b) Nabothian cyst, (c) island of columnar epithelium, (d) external os and (e) columnar epithelium.

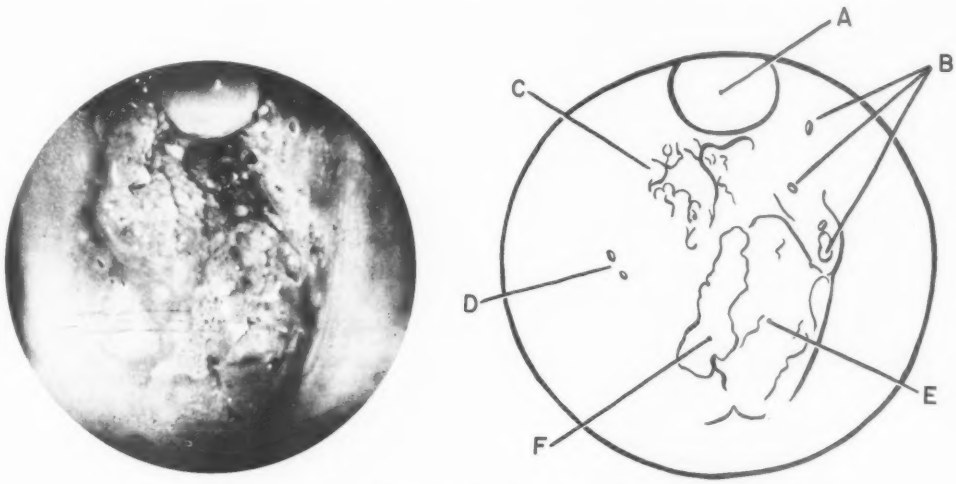

Fig. 3. Colpophotograph and accompanying diagram of colposcopic atypisms of a pregnant portio. Shown are: (a) mucous plug, (b) gland islands, (c) columnar epithelium, (d) gland openings, (e) columnar epithelium with mosaic leukoplakia superiorly, (f) simple leukoplakia at the tip, ground leukoplakia above. Cytologic smear was Class II, histologic pattern was benign.

Colposcopy does not supplant the cytological technique in evaluating the portio of pregnancy, but it does add to the information gained. As with cytology, biopsy is the decisive and definitive procedure. The major advantages of colposcopy are that it gives an overall view of the portio, indicates when grossly "suspicious" findings may be benign and aids in locating the desirable site of biopsy.

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DISCUSSION

FRIEDRICH BAJARDI, Graz, Austria:

From longstanding experience in colposcopy I can only agree with Bret that during pregnancy some changes of the epithelium are more easily detected than in non-pregnant cases. These are, above all, to be found in the so-called "matrix zones" (simple leukoplakia, mosaic leukoplakia and ground leukoplakia). In addition to a thickening and spreading of the surface area of leukoplakias, the marked difference in color between the purplish squamous epithelium and the white leukoplakic area very often facilitates a diagnosis.

However, on the other hand, colposcopy can be more difficult during pregnancy as compared with the non-pregnant state. In my opinion these difficulties arise from physiological changes of the cervix during pregnancy, a fact which has already been widely dealt with by the main speakers. Increased vascularization and hydration of the stroma in combination with a hyperplasia of epithelial tissues are typical findings during pregnancy, but these can be seen as well in cases of malignancy. If, however, such changes in pregnancy appear associated with other benign lesions of the cervix, for instance, if they are found in the ectopy or transformation zone, it might be very difficult to recognize such lesions as benign ones. In these cases biopsies that could otherwise be substituted for by colposcopy, will be absolutely indispensable.

Furthermore, I would like to call special attention to the atypical transformation zone whose appearance has been described above by Lang. From my own experience this finding is most important in the detection of pre-clinical carcinomas, demonstrating suspicious changes in almost 40% of colposcopically detected cases. The histological background of these yellow, glassy-looking transformation zones was recently described (1). There might be alterations in the surface epithelium or even changes in the subepithelial tissues which cause a decrease in transparency of the tissues in question.

In case of pregnancy, atypical transformation zones were rather frequent in our material. As could be proven by histological examinations of the biopsies from these transformation zones, the reason for the yellow, glassy appearance of the epithelium during pregnancy was very often a decidual reaction of the subepithelial tissue.

Thus, the atypical transformation zones during pregnancy seem to offer less opportunity for suspecting cancer than in non-pregnant cases. Nevertheless, biopsies should be taken from the site of any changes for the purpose of proving or disproving malignant epithelial growth.

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ROBERT GANSE and RAIMUND KRIMMENAU, Dresden, Germany:

During pregnancy one frequently finds ectopies. The more intense blood circulation and hydration of the tissue cause a marked accentuation of the ectopic grape-like structures and of the papillae of the squamous epithelium. Metaplastic changes at the squamo-columnar junction are more frequent during pregnancy. The most difficult differential diagnoses to be made are on inflammatory lesions with marked tendency to bleed.

Those colposcopic changes (compatible with the "atypical epithelium" of Hinselmann) which are already present before pregnancy become coarser and more vascularized, e.g., the "Ground" as well as the "Felderung" looks more elevated. The judgment of colposcopic findings shortly prior to term becomes difficult because of the vulnerability of the tissue. We have found recurrent papillomas of the cervix during two subsequent pregnancies. Various papillomatous lesions are more often found during pregnancy, e.g., condylomata. Such lesions heal quickly by overgrowing squamous epithelium. Every colposcopic diagnosis during pregnancy, therefore, has to be evaluated very cautiously.

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OTAKAR NYKLÍČEK, Náchod, Czechoslovakia:

Colposcopy in pregnancy has its justified significance and permits the observation of the uterine cervix and of all changes that arise during pregnancy or those that existed previously and develop further or aggrevate.

The fact that cervical carcinoma is more frequent in multiparous women than in the nullipara, in addition to the studies by Hamperl, Kaufmann and Ober (1954), justify the concentration of attention on "prebioptic" methods of examination; namely colposcopy and cytology.

The colposcopic findings in pregnancy are, as a whole, the same as in non-pregnant women, only the characteristic color caused by hypervascularization and epithelial hyperplasia is different, as Lang, Brèt and Coupez point out. I believe, therefore, that the nomenclature should remain the same as in non-pregnant women, namely the original one by Hinselmann.

I consider it very important to observe the "transformation zones" ("Umwandlungszone" of Hinselmann).closely during pregnancy and even more closely after delivery.

The ectopies originating in pregnancy heal either by squamous epithelium growing in from the periphery or by indirect, regenerative metaplasia. During these processes, which are accelerated during pregnancy, there is a possibility of pathological differentiation in the transformation zones.

In order to show the progress of healing of ectopies in the colposcopic picture, we have divided the transformation zones into three groups:

Transformation Zone No. 1: It marks the beginning healing process. In the colposcope we see the tongue-like stripes of squamous epithelium growing from the periphery into the areas of columnar epithelium.

Transformation Zone No. 2: It marks an advanced healing process. We see an apparent picture of epithelial metaplasia: open glandular ducts, small and large retention cysts or patches of columnar epithelium.

Transformation Zone No. 3: The healing process is completed. The entire cervix is again covered with squamous epithelium, in which the open glandular ducts or older retention cysts persist, consisting of the original columnar epithelium.

The vessels play an important role in the development of carcinoma. Colposcopy, in its present stage, permits observation of the behavior of capillaries, particularly at the base of leukoplakias and the manifestation of adaptive vascular hypertrophy. I believe that it will be possible to diagnose the early stages of cervical carcinoma even more precisely when the colposcopes are technically improved.

HANS-ISELIN WYSS, Zürich, Switzerland:

In our hospital we perform the so-called "extended" colposcopy examination (colposcopy + iodine test (Schiller) + surface biopsy (Schiller) in suspicious cases) also during pregnancy.

During pregnancy the squamo-columnar junction is very often shifting towards the outside of the cervix and therefore can easily be inspected with the colposcope. In more than half of the pregnant women examined, we found a more or less large ectopy and were able to study the border between the squamous and columnar epithelium. In non-pregnant women this junction is often within the endocervix and therefore not exposed to visual inspection.

Comparing the normal colposcopic pictures of pregnant and non-pregnant women, we found the differences described by Bret and Coupez. The distribution of the suspicious colposcopic findings (bleeding ectopy, bleeding zone of transformation, true erosion, ulcerations, polyps, uncharacteristic iodine-negative areas with sharp borders, matrix areas, leukoplakia, mosaic leukoplakia, ground leukoplakia, abnormal transformation zone) did not show any difference in relation to non-pregnant women. However, we are unable to give detailed figures on the frequency of suspicious findings in non-pregnant women, since we have no series for comparison. The relationship between their colposcopic and histologic findings corresponds absolutely to our results in non-pregnant women.

In a series of 485 pregnant women, who were examined between the third and the fourth month of pregnancy and in which two biopsies of the cervical os at twelve o'clock and six o'clock were taken, we obtained the following results:

Total number of cases: 485

	Surface biopsy (Schiller) indicated 146	Surface biopsy (Schiller) not indicated 339
Unsuspicious epithelium (incl. basal cell Hyperact. BCH I-(II))	138	335
Dysplastic ("unruhiges") epithelium	3	3
Cases of atypical epithelium (not classified)	2	0
Carcinoma in situ	3	1

It is obvious that four patients with suspicious histological changes were missed on colposcopical examination: one carcinoma in situ and three with dysplastic epithelium. Positive results were found in eight cases.

The following table shows the relationship between colposcopic and histologic findings. It corresponds with the results we found in a larger series of non-pregnant women.

	Bleeding Ectopy, bleeding transform. zone	Polyps	Unchar. iodine neg. sharp border zone	Matrix areas	Abnorm. transform. zone	Susp. of tumor	Special cases	
Unsuspicious epithelium (incl. basal cell hyperact. BCH I -(II))	4	10	60	60	1	1	2	138
Dysplastic ("unruhiges") epithelium (BCH III)			1	1	1			3
Cases of atypical epithelium (Not classified)			1	1				2
Carcinoma in situ			2	1				3

CLOSING REMARKS

WARREN R. LANG:

I concur fully with the discussors, all of whom stress to some degree or other the necessity for caution in evaluating the pregnant cervix colposcopically because of the physiologic changes which occur. Our own feeling is that if there is any suspicion on a clinical, cytologic or colposcopic basis, biopsy should be done. We have experienced no serious difficulties from frequent excisions of cervical tissue for histologic study.

COLPOMICROSCOPY ON NORMAL AND ABNORMAL EPITHELIAL AREAS DURING PREGNANCY

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During pregnancy, the colpomicroscope reveals mainly cells of the intermediate type, which is due to the high degree of progesterone production. Frequently, the regularity of the chromatin content of the nuclei disappears, and quite often one may notice a "salt and pepper-like" structure. Besides cells of the superficial type, intermediate type cells are often found during the first few weeks of pregnancy. At the beginning and at the end of pregnancy the cellular outlines are rather sharp, and about the fifth and sixth months of pregnancy they are slightly indistinct.

In one-third of all pregnant women, ectopies can be clinically observed. In the colpomicroscope they appear as glandular, often papillary, erosions. Contrary to ectopies in cases of non-pregnant women, the above ectopies give "unclear" pictures. This is caused by an increase of fluid, in both the nucleus and the cytoplasm. We have experienced that the colpomicroscopic examination becomes more difficult when an increased production of mucus exists. At the end of pregnancy the leukocytes, as well as the exfoliation of the cells, are increased, and thus, the diagnosis by means of colpomicroscopy becomes more difficult. Quite often atypia of the squamous epithelium can be seen on the rim of such ectopies. For the less experienced examiner, such findings might appear overly suspicious for carcinomas, but these cases ought to be followed up colpomicroscopically, cytologically and colposcopically. In case the atypia persist or show increased irregularities, a biopsy should be performed during pregnancy.

In our material of recent years only a few cases were found which made a histologic verification necessary during pregnancy because of a false positive colpomicroscopic diagnosis.

In some cases, however, such very marked epithelial atypia are observed which are characteristic for a squamous carcinoma: increased number of cells, polymorphism, polychromasia, irregular position of the nuclei, pathologic mitoses and highly developed irregularities of and noticeable increase in the chromatin content. Histology sometimes shows carcinoma in situ, as in the following case:

Thirty-seven year old patient with the following history: gravida IV, para III, miscarriage I. Normal menstrual flow before last pregnancy. No serious diseases. The patient was admitted to the hospital because of indifferent pains in the lower abdomen in the third month of pregnancy. The inspection of the cervix revealed an unsuspicious erosion together with cervicitis. The early cancer detection methods, routinely practiced at our clinic (cytology, colpomicroscopy), resulted in a positive report (Papanicolaou Class IV). Therefore, a biopsy was performed at the area of the most developed atypia found in the colpomicroscope. Histologically: carcinoma in situ with involvement of endocervical glands. The last postoperative reexamination did not reveal any malignancy.

On the other hand, it is possible that histology sometimes reveals an already invasive squamous carcinoma, as shown with one of our cases:

Forty-two year old patient: gravida III, para II, miscarriage I. Before the last pregnancy normal menstruation and no serious diseases. During the second and third month of pregnancy the patient noticed a whitish-yellow discharge. Colposcopy, colpomicroscopy and cytology were positive. The reports remained positive. In the seventh month of pregnancy mainly based on the colpomicroscopic examination, biopsy with the cold knife was performed. Histologically: invasive squamous carcinoma. Shortly afterwards a Caesarean section, followed by a Wertheim radical operation, was carried out. The histologic examination of the specimen revealed a partly in situ, partly invasive squamous carcinoma.

Based on the above two cases and the mentioned findings, it is understandable that the colpomicroscopic diagnosis "suspicious for carcinoma" should be made with great caution, especially during pregnancy. A similar cautious diagnosis in cytology and in colposcopy is necessary when suspecting a carcinoma during pregnancy. Even histology cannot always differentiate between benign, mostly inflammatory, changes of squamous epithelium and carcinoma.

In spite of some difficulties, especially during pregnancy, colpomicroscopy is of great advantage, mainly because pathologic changes on the surface of the cervix in the living are under control without biopsy.

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In order to establish the variations occurring on the surface of the vaginal epithelium during pregnancy, we have examined 176 pregnant women by colpomicroscopy, colposcopy and cytology, with the aim that through combination of these three methods a maximum of exact observations could be obtained. Frequently, differences could be found between cytological and colpomicroscopical results. In our opinion, these differences originated from the fact that cells are more readily subject to exogenous influences after their exfoliation than when within the epithelial surface. In addition, the fixation and staining for cytological examination changes the shape of the cells; while for the colpomicroscopical examination, because of staining in vivo and in situ, such influences do not exist.

The following points are the basis for our judgment of colpomicroscopical examinations: size of cells, existence or nonexistence of cell boundaries, tendency of cells to exfoliate from the epithelial surface, intensity of coloring, size and shape of nuclei, position of cells, i.e., of cell nuclei relative to each other, deviations of nuclear shape and polynuclear cells. We have stained with 1% toluidin blue solution in most cases. In some we used a 1% solution of Evans blue as control. All colpomicroscopical photos were taken on the patient in situ. In the case of 82 patients, the colpomicroscopical findings were fixed photographically, in each case for about four or five different areas. For later examination this was extremely important, as our findings frequently differed considerably regarding the examined epithelial surface. For this reason we registered as the characteristic finding, the most frequent one.

I. Colpomicroscopical findings in cases of normal pregnancy

Colpomicroscopical findings during normal pregnancy can be divided into four main sections: A. first to third month, B. fourth to sixth month, C. seventh month until about a week before birth and

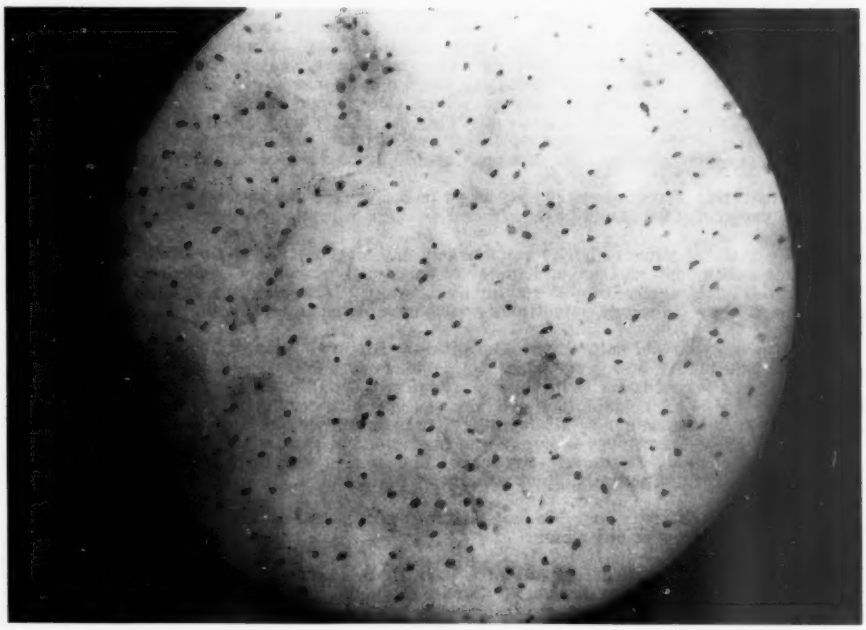

Fig. 1. Pregnancy second month. Near the upper edge of the picture a group of navicular cells, others mostly superficial cells.

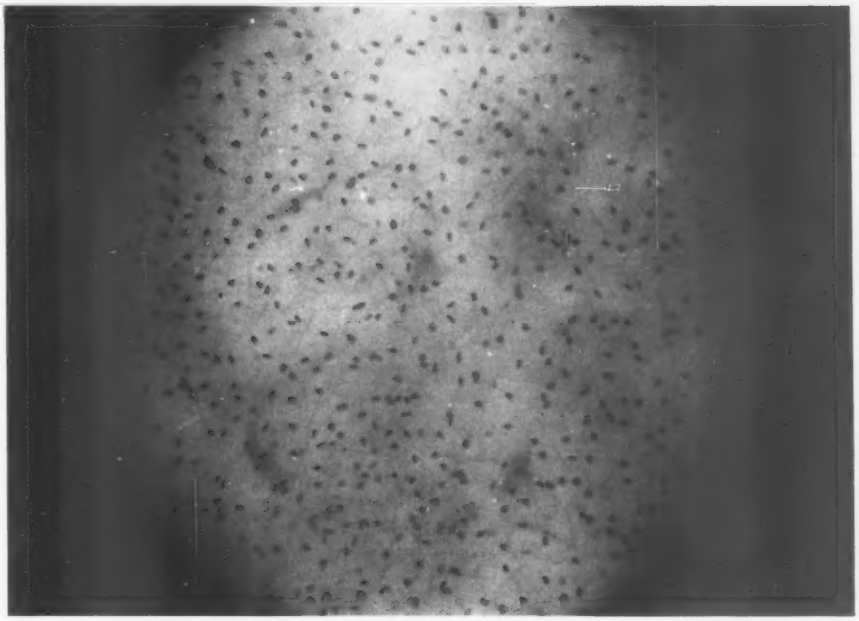

Fig. 2. Pregnancy fourth month. Explanation in text.

D. the last week before birth. Between the above sections, however, there are various transitions which can last up to two months.

A. During the first three months variation of the epithelial surface is little different from non-pregnant women. Cell boundaries are apparent. Cells usually are rather large, corresponding to the superficial type occurring on the vaginal smear. The cytoplasm is delicately colored, the nuclei are small, of ciruclar shape and frequently pyknotic. Interspersed are cells with curled edges. They are usually of more intense color and have a tendency to aggregate in small groups. The nuclei of these cells are either round and shaped like blisters or they are of spindle type (Fig. 1). These latter cells correspond to navicular cells. As a characteristic variation due to pregnancy, however, these findings cannot be used.

B. By the beginning of the fourth month, in some cases during the third month, the number of superficial cells decreases. The amount of cells on the surface is striking (Fig. 2). Cells are smaller and cell boundaries are easily visible. The color of protoplasm is more intense. Nuclei predominantly are relatively small and mostly round. The number of spindle-shaped nuclei increases somewhat. Sometimes single, large nuclei of blister shape, each with a distinct chromatin structure, are found. These increase in number toward the sixth month. Some single pyknotic nuclei are still found. This finding can be observed as late as the seventh month. Corresponding cytological findings in this period also show an increase of navicular cells. A definite type of clustering predominates during the fourth and fifth months. Towards the sixth month, cell clusters increase due to a stronger tendency of the cells to exfoliate. There is also a large increase in the number of Döderlein bacilli in the vaginal smear which causes cytolysis of the cells.

C. By the beginning of the seventh month or sometimes, however, as early as the fifth month, a considerable transition occurs on the epithelial surface. The transition usually takes place within a short period of time. It begins with a slow deterioration of the cell boundaries with the coloring still remaining rather delicate. The size of the nuclei is approximately the same as in the sixth month (Fig. 3). As the next step, the surface becomes a rather intense blue color and the cell boundaries almost completely vanish. In between, however, there are still some areas of less intense color where the cell boundaries are clearly preserved. The nuclei in the intensely colored areas are larger (Fig. 4). The corresponding cytological finding shows an increase of cell clusters. These cell clusters correspond in type to the navicular cells and probably stem from the areas of homogenous blue color. Besides these cell clusters, there still are a certain number of individual cells, usually larger than the navicular cells, which correspond to the normal intermediate type. By the end of the seventh month the cell boundaries have completely vanished. The whole surface of the epithelium is colored a more or less intense blue. The nuclei usually vary considerably between small, intense colored ones and large nuclei of more delicate color. In unusual cases, spindle-shaped nuclei predominate. These findings remain until a week before birth (Fig. 5).

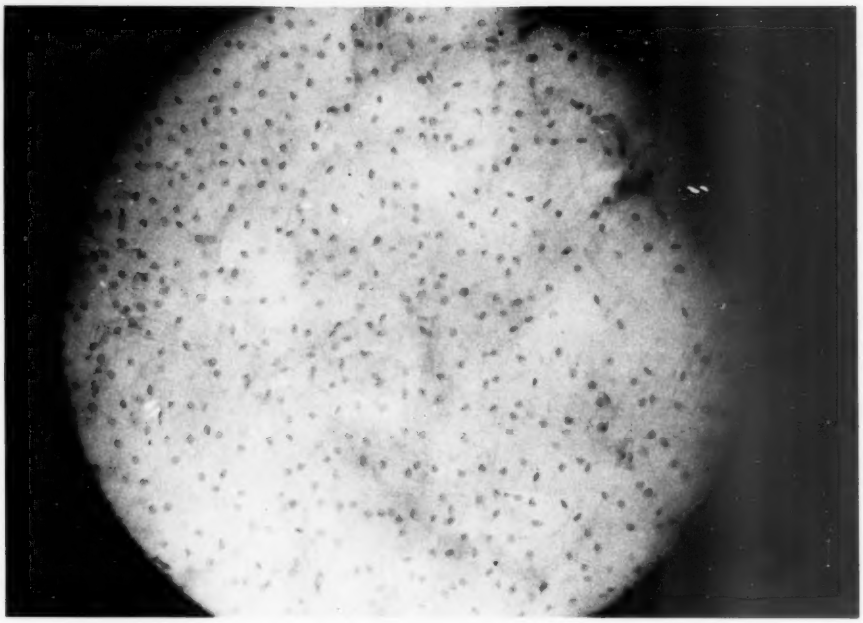

Fig. 3. Pregnancy seventh month. Rather dark homogeneous color. Cell boundaries vanishing. Nuclei predominately round, single spindle nuclei.

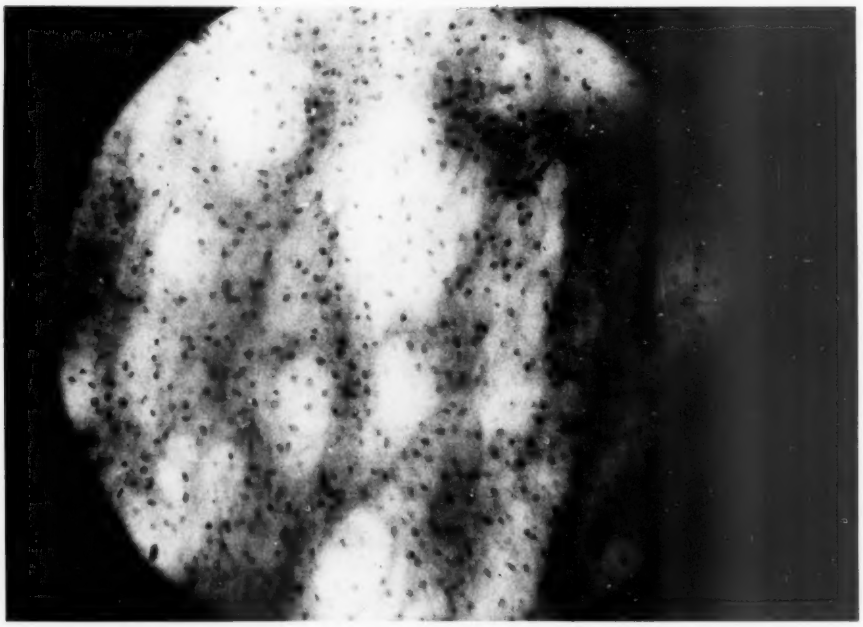

Fig. 4. Pregnancy eighth month. Explanation in text.

D. About one week before birth, certain variations occur on the epithelial surface. In twelve cases we had the opportunity of giving colpomicroscopical examinations continuously from the eighth day until the beginning of labor. In eleven of these twelve cases there was a certain conformity which permits some general conclusions. In six cases, about the fifth day before birth, large cells with light cytoplasm and medium-sized nuclei of intense color suddenly appeared. These cells were dispersed within the otherwise homogeneous dark surface (Fig. 6). In three of these cases, we could observe these cells as late as twelve hours before the beginning of labor. In the rest of the cases, observations could be continued only until two days before birth. In five other cases, another characteristic picture appeared. Here we found the nuclei (usually three to five) arranged in a chain-like formation. Furthermore, polynuclear cells (usually binucleated) appeared. We also observed large nuclei of intense color with a relatively large but not light cytoplasm (Fig. 7). On our cytological smears we could not discover corresponding variations. For judgment here we used the changes as found by Lemberg and Stamm, which, however, in our cases predicted the right date of birth only eight times. In one case the changes as decribed above could not be found.

During normal pregnancy we found a period in which cells on the epithelial surface had no boundaries. The smear revealed cells of this period situated predominately in groups, being of the navicular type. Particularly during this time vaginal smears frequently showed cytolysis. At the same time, an appreciable increase of Döderlein bacilli occurred. However, the cytolytic type (Wied) was found in the vaginal smear at other times too, i.e., on the epithelial surface, cell boundaries were clearly found, while exfoliated cells of the vaginal smear showed apparent signs of cytolysis. In these cases there was an additional invasion of cocci in the vagina without, however, further variations of the epithelium. This is rather important for the diagnosis, as variations of the exfoliated cells occasionally are considerable, while the epithelial surface is exempted from these changes. The appearance of cells on the normal epithelial surface does not change (independent of the stage of pregnancy) until more or less marked colpitis appears. In such cases a diminution of cytoplasm is found, cell boundaries usually are obscured and the distance between cells increases, which is particularly apparent during the stage of no cell boundaries. The nuclei are larger, being somewhat swollen. In general, the findings are comparable to the initial menopausal type. This inflammatory cell type was found by colpomicroscopy on the epithelial surface in about 2% of our cases; however, by cytological examination, they were found in about 5% of the cytological smears (Wied in 7.5% and Artner and Koller in 5%). Again, the explanation for this difference is the varience in sensitivity of the exfoliated cells towards exogenous influences as compared to cells in situ.

Variable findings on the epithelial surface in the area between the vagina and the cervix is rather frequent, particularly when an ectopia or an erosion exists. Surrounding this is a rather wide area, in which findings corresponding to the particular stage of pregnancy frequently cannot be found. But from this transitional part to the vaginal wall itself, the normal findings can be found, which is important for the diagnosis of the particular stage of pregnancy.

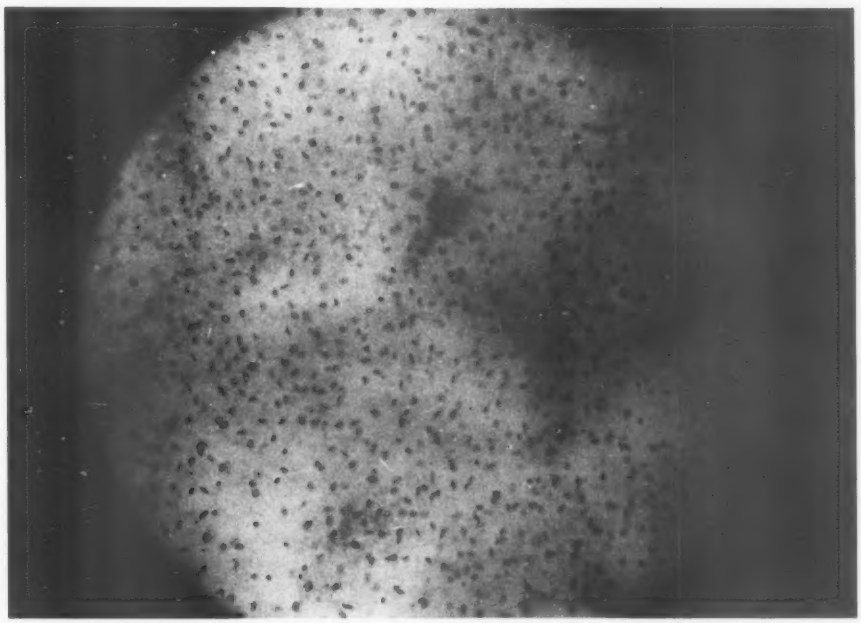

Fig. 5. Pregnancy eighth month. No cell boundaries, homogeneous blue colored, nuclei of varying size.

II. Findings in cases of abnormal pregnancy (abortion, etc.)

In our cases of imminent abortions, we could not find any significant differences on the epithelial surface in comparison to normal pregnancies, even in those cases where later abortions occurred. Similarly, in cases of imminent premature births no characteristic variations could be found.

III. Prolonged pregnancy

We had the opportunity to observe six cases of actual prolonged pregnancy, which all gave similar colpomicroscopical findings. In all of them, after the stage without cell boundaries, boundaries began to reappear slowly but clearly. The cytoplasm became lighter. There always were individual cell clusters in the otherwise uniform picture of the surface. The size of the nuclei varied between small, round, partly spindle-shaped ones and larger, round nuclei with significant chromatin structures (Fig. 8). These findings can be evaluated as prolonged pregnancy only if there are repeated observations covering some days or weeks. It is important that such findings be compared to earlier ones in the eighth or ninth month of pregnancy, in which cell boundaries have not yet vanished. Any such finding is proof for prolonged pregnancy only if the stage without cell boundaries has previously been passed through.

IV. Abnormal findings during pregnancy

A. Regenerative epithelium: In 90% of our cases there was an ectopy with a fairly wide regeneration zone surrounding it. While in the state of non-pregnancy the surface of the regenerative epithelium, depending on its structure, consists of uniformly basal, parabasal or intermediate cells. Cell variation can occur during pregnancy. Often nuclei are larger and intensely colored. Sometimes, even their shape is atypical. Confusion with carcinoma is not likely, however, if the surrounding area is used for examination (Fig. 9). Such atypical shapes vanish rapidly after birth.

B. Atypical epithelium: In 176 cases we had five women with small areas of atypical cervical epithelium. None of these atypical epithelia were so marked, however, that we had reason to suggest a malignancy. These areas were marked by cells, and particularly nuclei, which were polymorphic and polychromatic (Fig. 10). The border with the adjacent normal epithelium always was clearly marked. In three of the five cases the atypical areas of the epithelium vanished immediately after pregnancy. In two cases they still existed five months after birth. One case was histologically examined. The finding was basal cell hyperactivity.

C. Carcinoma in situ and invasive carcinoma: We have a number of earlier observations not identical with the 176 cases mentioned above. Colpomicroscopical examination of carcinoma in situ and invasive carcinoma during pregnancy did not show any significant difference compared with cases of non-pregnancy.

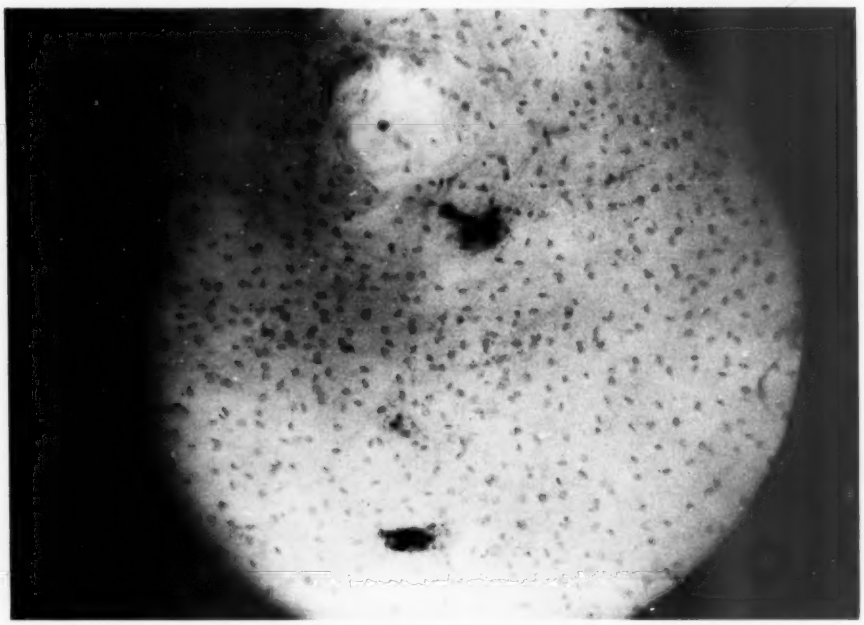

Fig. 6. Four days before birth. Within the homogeneously colored surface, one large cell in the upper half of picture.

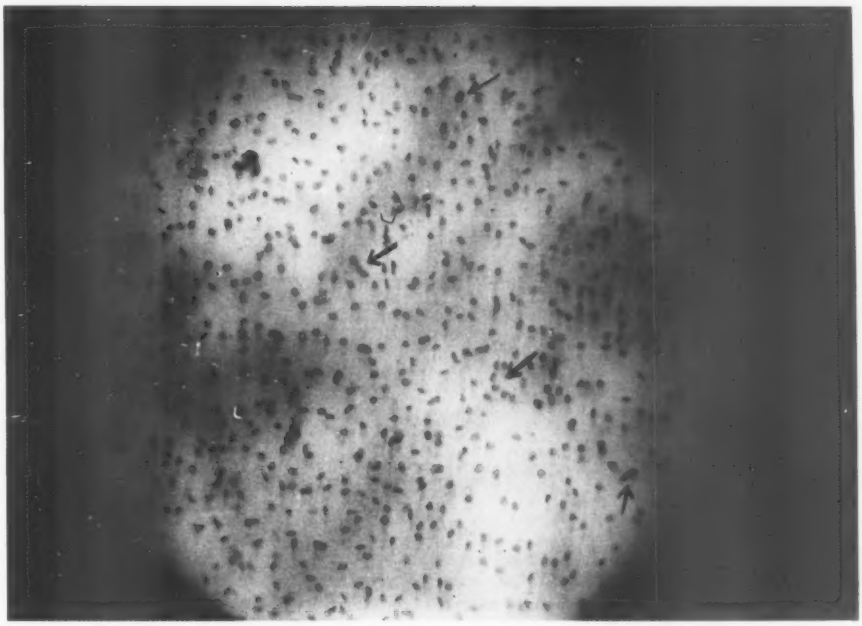

Fig. 7. Three days before birth. Nuclei arranged chainlike (3-5) and cells with two nuclei (see arrows).

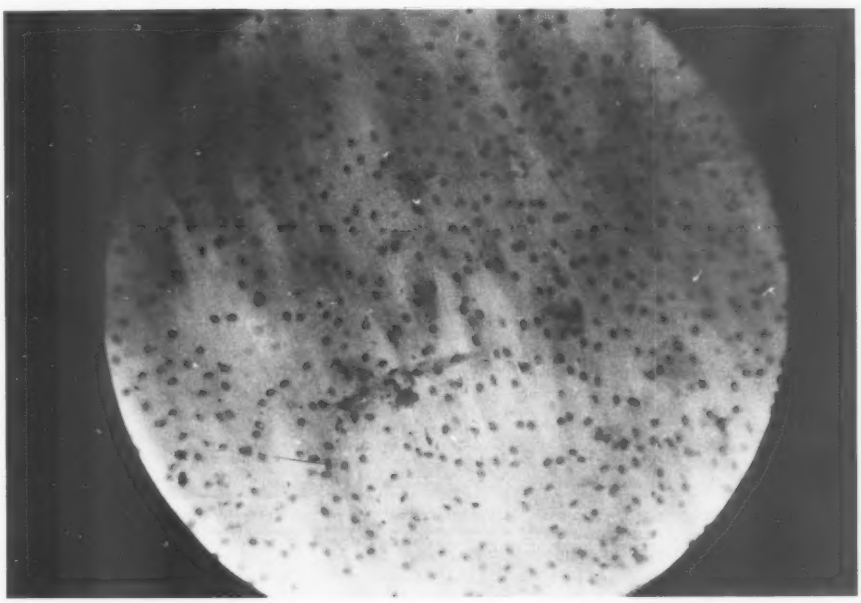

Fig. 8. Two days before birth. Birth delayed 21 days. The new-born bearing significant signs of delayed birth. Cell boundaries reappear. Individual cell clusters on the surface.

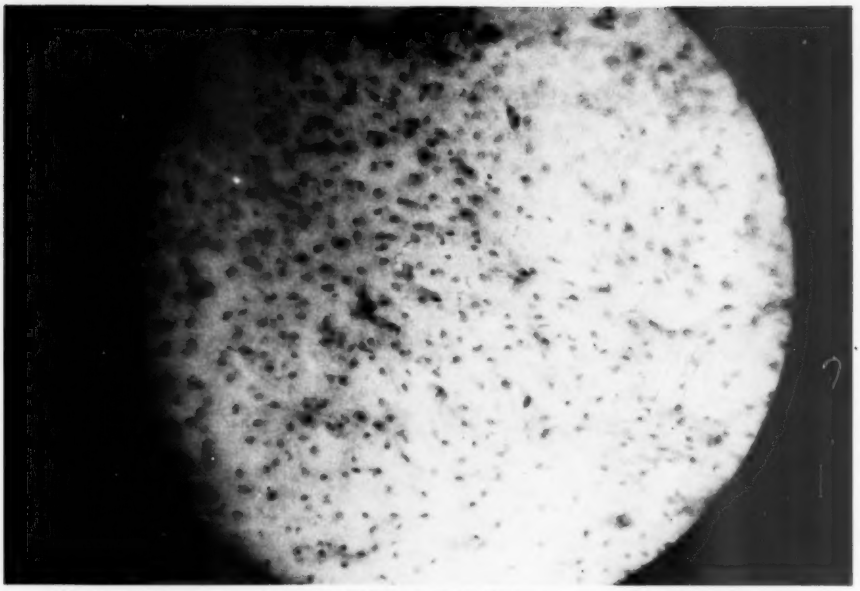

Fig. 9. Pregnancy fourth month. Left part of the picture regenerative epithelium. On the surface predominately parabasal cells. In between single large atypical nuclei.

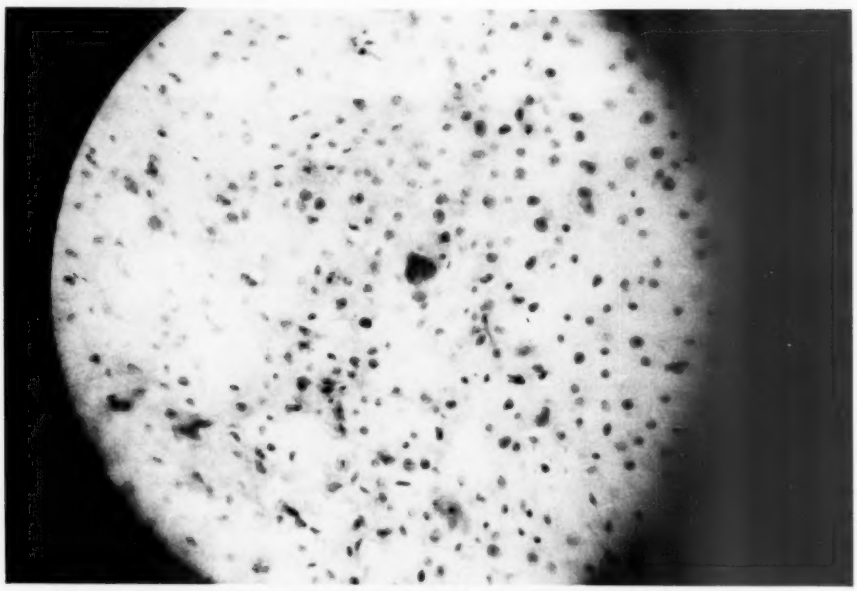

Fig. 10. Pregnancy ninth month. Atypical epithelium recognizable by the polymorphic and polychromatic form, mainly of the nuclei. Histologically five months after birth: basal hyperactivity.

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EXFOLIATIVE CYTOLOGY OF INFECTIONS DURING PREGNANCY

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The bacteriological examination of cervical or vaginal smears permits the recognition of the following six types of infections, according to Wied (1):

Vaginal smears with mainly Bacillus vaginalis Döderlein.
Vaginal smears with mixed flora.
Vaginal smears with mainly cocci.
Vaginal smears with Trichomonas vaginalis.
Vaginal smears with fungi.
Vaginal smears without visible bacteria.

Bacillus vaginalis is a very frequent organism in the vagina of pregnant women and is responsible for the cytolytic type of smear, which in our series was observed in up to 28% of our pregnancy smears during the 16th week of gestation. It produces no inflammatory changes and does not seem to have any harmful effect upon the pregnancy except the development of a colorless or whitish discharge. Smears with a mixed bacterial flora, or with predominatly cocci, usually contain an increased number of polymorphonuclear leukocytes, and the epithelial cells show the dyskaryotic changes typical of inflammation (2,3). The presence of Trichomonas is often associated with severe nuclear dysplasia in the squamous and columnar epithelial cells which sometimes may lead to the erroneous diagnosis of a malignant process (4). Candida albicans and Leptothrix vaginalis are the two most common fungi found in the vaginal secretion and may produce cellular reactions resembling those associated with Trichomonas.

In order to study the cytological picture of infection during pregnancy, we have compared the findings of 200 smears taken during the 16th to 18th week of gestation with 200 smears of normal menstruating women under 40 years of age and 200 smears of women in natural menopause (ages 55-76). All smears were obtained by cervical scraping. Our results are listed in the following table.

Table 1

Percentage Distribution of Inflammatory Changes and Bacterial Infection during Normal Menstruation, Pregnancy and Menopause

TYPE OF SMEAR	CYTOLOGIC EVIDENCE OF INFLAMMATION				MICROBIOLOGIC CLASSIFICATION (WIED)					
	None	Mild	Mod.	Severe	None	Bac. vag.	Mixed Flora	Coccal Flora	Trich. vag.	Fungus
Highly proliferated Preovulatory	53	25	13	9	22	46	20	4	6	2
Navicular Pregnancy	32	40	16	12	21	31	25	5	17	1
Atrophic Menopause	17	61	14	8	26	4	49	8	9	4

From this table it is evident that the highly proliferated preovulatory smear of the normal menstruating woman shows the least evidence of inflammatory changes and the highest incidence of Bacillus vaginalis. Smears from pregnant women showed a higher incidence of inflammatory changes and a higher incidence of Trichomonas infestations. Smears from women in the menopause showed the highest incidence of inflammatory change with prevalence of a mixed bacterial flora. The navicular cells characteristic for pregnancy assume a high degree of eosinophilia in the presence of inflammatory changes without losing the pale and vesicular appearance of the nuclei. The number of parabasal cells seems increased and the cells appear larger and possess a denser staining and often eosinophilic cytoplasm. Inflammatory changes during pregnancy tend to make the vaginal smears indistinguishable from the inflammatory smears of non-pregnant women.

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The normal bacterial flora of the human vagina consists of varying numbers of Döderlein bacilli, partly influenced by the physiologic state of the woman. The amount of Döderlein bacilli may vary during the cycle with an increase during the latter part of the secretory phase. A marked increase may often be seen during pregnancy associated with marked cytolysis, while a decrease in Döderlein bacilli is usually found during the postmenopausal age. The presence of large numbers of Döderlein bacilli is generally considered as a grade of high purity ("Reinheitsgrad" No. 1). Mixed infections characterized by the presence of other bacteria in addition to Döderlein bacilli are not infrequently seen. It is, though, rarely associated with infections due to Trichomonas, Monilia, Leptothrix or coccoid bacteria. It is also rarely found in the presence of cervical carcinoma.

In view of the fact that cytolysis associated with Döderlein bacilli affects solely one cell layer of the epithelium, and thus prevents the maturation of cells above the upper intermediate layer, the hormonal evaluation in such cases during pregnancy is difficult.

The profuse presence of coccoid bacteria is not infrequently encountered in vaginal smears of pregnant women. It is usually associated with predominantly karyopyknotic cells, although hormonal production may be normal. Therefore, during pregnancy the presence of coccoid bacteria and a high Karyopyknotic Index is not necessarily an indication of progesterone deficiency and impending abortion.

Trichomonas infection usually results in increased eosinophilia of non-karyopyknotic cells and the presence of a perinuclear halo. The presence of Leptothrix vaginalis is relatively infrequent and often associated with Trichomonas infection as well as coccoid bacteria. The cellular changes are usually those found with coccoid bacteria and Trichomonas. Infestations with Monilia albicans are often associated with a slight irregularity in the borders of normal-sized nuclei. Cervicitis is often associated with slight nuclear abnormalities such as increase in size and a homogeneous deeper staining reaction of the nuclei of superficial and upper intermediate cells. There may be multinucleation usually presenting uniform nuclei often without an increased staining reaction, and particularly a uniform binucleation may be found in well-differentiated endocervical cells, due to marked cervicitis.

In addition to the effect of the invading organism on the cells, the morphologic alterations depend on the hormonal status of a woman, and in accordance with this, on the type of epithelial growth. In pregnancy the increased activity of hormones may, in addition to increased proliferation of epithelial cells, also produce benign epithelial changes such as basal cell proliferation, reserve cell proliferation and increased endocervical cell proliferation with resulting changes of hyperplasia.

The effects of infection on cells of an altered epithelium under increased hormonal stimulation may at times result in the finding of equivocal types of cells in cervical smears. In the diagnosis of carcinoma the same strict criteria should be applied as in the non-pregnant state, and no diagnosis of malignancy should be rendered unless the irregularities of the nuclear structure and of the nuclear-cytoplasmic ratio in cells of the parabasal type are known to be unequivocally characteristic for carcinoma.

The application of such criteria to the abnormal cells of infection, in the presence of epithelial pregnancy changes, usually prevents a possibly false interpretation of these cells.

DISCUSSION

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Dr. von Haam did a comparative study of the modifications of the cytology of infections in the pregnant and non-pregnant woman, based upon the microbiological classification of Wied. I now ask which method Wied has followed for his microbiological classification, the one of Papanicolaou or the differential methods of bacteria, as the Gram staining procedure, cultures, etc. I say this because the Papanicolaou method only orients, and is not a good estimation as to the precise bacteriological diagnosis. This latter point is important for proper treatment. At this time we cannot discuss the non-pregnant bacteriological classification, because we will then be too far removed from our main topic.

We partially agree with Nieburgs since we have seen infection alter the cytology of pregnancy in such a way that the navicular cells and the cytolysis produced by Döderlein bacillus of the normal pregnancy both disappear.

In coccoid infections we see an increased eosinophilia, but not a Karyopyknotic Index as Nieburgs has observed. We have seen that many of the alterations produced by Trichomonas infections produce a smear that is not at all similar to that of normal pregnancy. The above mentioned smears show a marked dyskaryosis and eosinophilia of the intermediate and parabasal cell layers.

Recently we saw two cases of pregnancy with smears exhibiting Trichomonas infection associated with Döderlein bacillus. This is not strange, because the Trichomonas have the same developmental conditions as Döderlein bacillus, e.g., vaginal epithelium rich in glycogen making it easily accessible to bacteria (1) as occurs in pregnancy.

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CLOSING REMARKS

EMMERICH von HAAM:

The microbiological classification of Wied is admittedly not very accurate, although Bret with his many cultures and sub-cultures (see his paper in this symposium) finally relies upon a classification not unlike that of Wied. We have used it because it best illustrates the cytological variations caused by the various types of vaginal flora in pregnant women.

EXFOLIATIVE CYTOLOGY OF DYSPLASIA DURING PREGNANCY

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Among 6,652 pregnant women who had cytological examinations, 38 had dysplasias of the cervix which were diagnosed by means of histology. This series was classified as follows:

Among 12 benign dysplasias, the cytological report was:

1 Class IV which should have been Class III
6 Class III
5 Class II

Among 19 dysplasias warranting follow-up, the cytological report was:

8 Class III
11 Class II

Among 7 highly suspicious dysplasias:

1 Class IV
6 Class III

1. Cytology of benign dysplasia

The only Class IV smear in this series was an error on our part. When rescreened, no malignant cells were found. Instead we observed only atypical cells with well-preserved cytoplasm and enlarged, irregular nuclei. The smear should have been Class III.

The six Class III smears showed squamous cells with a well-preserved cytoplasm. The nuclei were large with perinuclear halos and well-preserved nuclear membranes. Very often the cytoplasm was orange.

In the five Class II smears, although the nuclei were in no way suspicious, we noted that many cells had yellowish-orange cytoplasm.

In this group:

8 cases were not followed.
3 cases were not treated but were followed on the basis of vaginal and cervical smears. The smears became negative (the Class IV case was included in this series).
1 case still has Class III smears a month after delivery.

2. Cytology of dysplasia warranting follow-up

The eight Class III smears showed squamous cells with well-preserved cytoplasm and enlarged, irregular nuclei. Most of these cells were superficial or intermediate cells.

In the eleven Class II smears, although the nuclei were not suspicious, we found cells with yellowish-orange cytoplasm. This was particularly noticeable in pregnancy smears, where the Eosinophilic Index is extremely low.

In this group:

15 cases were not followed (11 Class II and 4 Class III).
1 had negative smears in the follow-up, although she remained untreated.
3 had negative smears after a conization was performed.

3. Cytology of suspicious dysplasia

The Class IV smear was rescreened recently and although the biopsy revealed no evidence of malignancy, we still maintain that some of the atypical cells found indicate a carcinoma in situ. This case has been followed for over a year now by means of smears and has consistently shown highly suspicious cells.

In the six Class III smears two cases had Trichomonas infections which are often a cause of error. In these six cases the smears showed cells with yellowish-orange, well-preserved cytoplasm and enlarged non-homogeneous and hyperchromatic nuclei. The hyperchromatism has only been found in this group of suspicious dysplasia Class III smears, as compared to the Class III dysplasias which are benign or to be followed.

In this last group:

5 were untreated and followed by means of smears:

1 became negative.
4 remained Class III up to one year later.

2 had a conization and negative smears afterwards.

The conclusion of this study is that in the cases of suspicious dysplasia we had no negative smears. Also, the nuclear alterations seemed more significant. And finally, in all dysplasias, with Class III or II, we have found cells with yellowish-orange cytoplasm which is infrequent in pregnancy smears.

COMPARISON OF DYSPLASIA OF THE CERVIX IN PREGNANT AND NON-PREGNANT WOMEN

Among 25, 681 non-pregnant women 134 cases of dysplasia have been diagnosed. We have divided these as in the cases of pregnant women:

46 benign dysplasias with cytological reports as follows:

30 Class II
16 Class III

58 dysplasias warranting follow-up:

13 negative smears
34 Class III
11 Class IV

30 suspicious dysplasias:

19 Class III
11 Class IV

1. Cytology of benign dysplasia

Among the 16 Class III, four cases had a Trichomonas infection. The predominent characteristic of the abnormal epidermoid cells is well-preserved cytoplasm and enlarged nuclei.

In this group:

6 were not followed.
1 had a hysterectomy because of a total prolapse. She was 76 years old.
4 had a conization:

3 of these cases had negative smears afterwards.
1 was not followed.

5 were followed on the basis of smears:

4 had negative smears.
1 had Class III smears for 2 years.

2. Cytology of dysplasia warranting follow-up

The eleven Class IV have been rescreened. Three cases now appear to have actually been Class II and apparently our diagnosis at that time was overly pessimistic. The other eight cases, even now and in spite of the pathological report, exhibit malignant cells which tend to be in favor of a carcinoma in situ.

The 34 Class III cases showed intermediate and sometimes immature cells with well-preserved cytoplasm, which in 18 cases appears to be yellowish-orange.

In this group:

14 were not followed (1 Class IV and 13 Class III).
5 had a cauterization of the cervix and the following smears were negative (1 Class IV and 4 Class III).
17 had a conization in which (6 Class IV and 11 Class III):

16 cases had negative smears afterwards
1 case had Class III smears for two years and then negative smears.

1 had an amputation of the cervix followed by negative smears.
3 had a hysterectomy:

1 for an ovarian cyst and a hematosalpinx.
2 for unknown reasons.

5 were followed by means of smears:

4 had negative repeat smears.
1 case remained Class III.

3. Cytology of suspicious dysplasia

The eleven Class IV cases had smears which have been rescreened. In three cases the cytological diagnosis was exaggerated, and in eight cases the smears showed evidence of malignancy (the epidermoid cells were well-differentiated in three cases and poorly differentiated in five cases).

The smears of the 19 Class III cases showed mostly atypical parabasal cells, and the nuclei (as in pregnant women) presented a certain hyperchromasia which was not found in the benign and to-be-followed dysplasias.

In this group:

9 were not followed.
3 were followed by means of smears and were all negative.
11 had conization and were followed by means of smears:

9 had negative smears.
1 had Class III smears for 2 years which then became negative.
1 had Class III smears followed by a hysterectomy for a fibroid tumor.

3 had a cauterization of the cervix followed by negative smears.
4 had a hysterectomy.

4. Conclusion

In the two series of pregnant and non-pregnant women there were certain common characteristics:

a. In the cases of benign dysplasia (a total of 58), there were no Class IV smears, except for one in which we discovered an error when rescreened.
b. In the suspicious dysplasias, there were no Class II smears.

The cytological aspect of the abnormal cells is the same in these cases of dysplasia whether the patient is pregnant or not.

We feel that in most of our 24 Class IV cases our interpretations were justified even when the slides were rescreened. This is exclusive of the seven cases which should have been Class III, which were expected to show an intra-epithelial carcinoma. But the limit between a suspicious dysplasia and intra-epithelial carcinoma is as uncertain as the difference between a highly suspicious Class III and Class IV. We are treading on a razor blade !

EMMERICH von HAAM
Columbus, Ohio, U.S.A.

Overactivity of the basal cell layer of the stratified squamous cell epithelium in the cervix of pregnant women is responsible for the appearance of dyskaryosis and abnormal parabasal cells in about 20 per cent of cervical smears, according to Novak (1). These changes have been extensively studied by Walters and Reagan (2), who came to the conclusion that they are essentially similar to those observed in dysplastic lesions of nongravid women. They found a high percentage of agreement between the cytological and histological diagnosis of cervical dysplasia. A careful follow-up showed that 38 out of 63 lesions either regressed or were removed with the biopsy, while 21 persisted for a period of 7 to 65 months. Three cases of carcinoma in situ and 1 case of invasive carcinoma developed in this group.

In our experience cervical dysplasia during pregnancy is not rare and covers a multiplicity of lesions. Reagan and co-workers (3) speak of "atypical hyperplasia of the uterine cervix" and divide their cases into lesions of slight, moderate and marked degree. Most of the lesions show irregular thickening of the layer of stratified squamous epithelium with obliteration of the rete pegs and a more or less pronounced hyperactivity of the basal cell layer. The latter extends often through more than half of the entire thickness of the cervical epithelium and individual parabasal cells can be found well up into the keratinized zone.

The most important cytological finding in our cases consisted in an increase in the number of parabasal cells, which sometimes made up 20 per cent of the cell population. Most of the parabasal cells were larger than the normal parabasal cells, showed round or oval, finely granular nuclei and dense and often eosinophilic cytoplasm. Vacuoles of varying sizes or fine granulations were also observed in the cytoplasm, while most of the nuclei appeared homogeneous and opaque or showed finely granular chromatin without clumping and without visible nucleoli. The cells appeared singly or in sheets and many stained eosinophilic. The intermediate cells were of both types, the typical navicular cells of pregnancy and the immature proliferative type developing from the differentiating parabasal cells with homogeneous cytoplasm and without intracellular glycogen or wrinkling of the cellular membrane. Whenever the latter type was numerous, the smears became indistinguishable from that of dysplasia in a non-pregnant woman. Dyskaryosis in the cyanophilic, karyopyknotic and eosinophilic, karyopyknotic superficial cells expressed itself by the presence of enlarged nuclei with coarse and prominent chromatin networks. Sometimes each of the cells possessed two or more nuclei. In addition to atypical eosinophilic, karyopyknotic superficial cells, anucleate squamous cells were usually present, some of which showed a highly orange-staining cytoplasm.

The most important criteria for differentiating the cytological findings of cervical dysplasia and those of carcinoma in situ are the maintenance of a low nuclear-cytoplasmic ratio in the atypical cells and the absence of the small cyanophilic cell with enlarged pyknotic nucleus (malignant basal cell).

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ROBERT E. L. NESBITT, JR., DORIS S. ROME AND ARTHUR A. STEIN
Albany, New York, U.S.A.

The use of the smear is of particular importance in screening pregnant women for cervical lesions because pregnancy puts certain limitations upon the time and frequency of diagnostic procedures, particularly histologic studies, and the amount of tissue that can be safely removed for study. Moreover, the close correlation of cytologic and histologic findings in cervical material, as well as the special value of the smear in detecting non-clinical lesions, justifies confidence in the smear alone as a screening technique. Histologic study of the cervices of pregnant women is restricted to patients in whom doubtful or positive cytologic findings are present and to those who have a target lesion.

It should be pointed out, however, that special knowledge and experience are required in the interpretation of cervical and vaginal smears in the pregnant woman. As pregnancy advances, the normal predominance of eosinophilic superficial cells decreases and cyanophilic intermediate or navicular cells gain dominance in the smear. The nuclei are generally larger, and there is a greater ratio of nucleus to cytoplasm than in superficial cells. Normally, the cells of the parabasal zone are rarely seen (1). The general pattern of the navicular cells is usually one of small, dense clusters. Many conditions that are commonly seen in pregnant women, however, tend to alter this normal picture. Some degree in inflammation is evident in the vast majority of smears taken during pregnancy. Local cervical infections tend to cause a persistence of eosinophilic cells. Moreover, the cervical discharge, the myriad of bacteria and inflammatory cells may result in thick smears that are difficult to interpret. Others are obscured by numerous red blood cells associated with cervical polyps or erosions. Histiocytes may be prevalent and can be mistaken for actively growing neoplastic cells. Occasionally,

Trichomonas infections during pregnancy produce a proliferation of parabasal cells that may be quite atypical in morphology. It is also well-known that the cervical and vaginal smears may reflect any hormonal imbalance existing during the early months of pregnancy. Moreover, the presence of bizarre parabasal cells, histiocytes and inflammation is common in cervical smears of the early postpartum period. There may be dense clumps of cells, many of which contain large nuclei and perinuclear vacuoles. Likewise, in the reproductive processes following abortion and a curettage, the vaginal smear may contain cells of bizarre and atypical shapes; macronucleoli and staining changes are pronounced and can be disturbing. In several of our cases of abortion, we have observed very atypical cells of the "embryonal type" in the vaginal smears and have suspected that they were of fetal or placental origin. These several features of genital tract cytology during and following pregnancy must be appreciated if one is to avoid a high incidence of doubtful or false-positive smears in his interpretations.

With experience, one can usually distinguish between cellular atypism associated with these benign conditions and true malignant disease of the cervix. It should be borne in mind that exfoliation reflects the general principle that as a lesion develops from the suspicious to the malignant, one notes an ever-decreasing percentage of mature cells which rise to the epithelial surface. Among the atypias of squamous epithelium not severe enough to be classified as carcinoma in situ, basal cell hyperactivity seems to be the most important (2). In a recent study of 1,019 patients who had been studied by simultaneous cervical smears and biopsies, there was a 68.5% incidence of basal cell hyperactivity (shown histologically) in 54 cases where there were false-positive smears, and 35.6% of the patients with doubtful smears showed basal cell hyperactivity in the biopsy (3). When these smears were carefully reviewed, it became evident that the majority should have been classified as Class II of Papanicolaou. Since there is usually adequate cytoplasm, the cells are not likely to give the picture of crowding of abnormal nuclei characteristic of malignancy. There is general cellular regularity with a slightly altered architecture, although certain cells may show marked disturbance with highly irregular architecture and nuclear anomalies. There is usually an intermixture of cells from all layers, but cell maturation is usually retarded. In many of these cases careful study shows that the atypism is confined to cells of the superficial and intermediate type and that the parabasal cells are quite normal in appearance. The relative nuclear area is larger than that observed for normal cells, but significantly less than that recorded for carcinoma in situ. The absence of cells of the parabasal, dyskaryotic type or small, dyskaryotic type should make one pause in interpreting a smear as malignant. On the contrary, when parabasal dyskaryotic cells are prevalent, one can usually demonstrate carcinoma by pathologic examination of the tissues.

TABLE I

CYTOLOGICAL FINDINGS IN PREGNANT PATIENTS - ALBANY HOSPITAL

Class of Smear	GESTATIONAL PERIOD									
	1st Trimester		2nd Trimester		3rd Trimester		Unknown		TOTALS	
	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent	No.	Per Cent
I	559	93.0	398	93.0	95	90.5	582	87.4	1634	90.8
II	42	7.0	29	6.8	10	9.5	83	12.4	164	9.1
III	---	----	1	0.2	--	----	1	0.2	2	0.1
IV	---	----	--	----	--	----	---	----	----	----
TOTALS	601	100.0	428	100.0	105	100.0	666	100.0	1800	100.0

The fact that these lesions may be distinguished with a high degree of success is apparent from a review of the cytologic reports from the cytology laboratory of the Albany Hospital (Table I). Among 1,800 cervical and vaginal smears, taken from women at various stages of pregnancy, 166 showed definite cellular atypism (9.2%). Of these, 152 were readily classifiable as Class II (benign atypia). The remaining 14 cases were more difficult to classify, because a significant number of the cells were markedly atypical. A majority of the cells had lost the configuration and characteristics ascribed to their particular layer and had undergone nuclear or cytoplasmic alterations. Most of the cells were of the parabasal type with enlargement and hyperchromasia of the nuclei. Although the chromatin pattern was dense and the nuclear-cytoplasmic ratio was disturbed, these cytologic features were less marked than one usually sees in carcinoma in situ. After careful evaluation of these smears, only two were interpreted as Class III and none were classified as malignant. These patients are now being followed by repeat smears and tissue studies, when indicated, to learn the source and significance of these atypical cells.

It is our clinical policy to subject women with "doubtful" cervical or vaginal smears to tissue examination. It has not been our policy to distinguish between "suspicious" and "malignant" lesions solely on cellular evidence. We believe that any significant change in desquamated cells should be explained on the basis of changes in their parent tissues. Moreover, we believe that the question of invasion is a histological one, although the cell compliment in carcinoma in situ is often distinctive from that in the clinical ulcerating stage of the disease. In the pre-invasive variety, the neoplastic cells usually have homogenous size and shape, the cytoplasm is generally cyanophilic, the chromatin is thick, and the nucleus is hyperchromatic with a round or oval shape. In infiltrating cancer, on the other hand, bizarre cell shapes and forms are common, the cytoplasm is usually eosinophilic and the nucleus has an irregular shape. The authors believe, however, that the diagnosis of invasion depends primarily upon the amount of tissue available for histological study. Even in pregnant women an adequate ring biopsy about the circumference of the squamo-columnar junction should be taken in these cases to prove malignancy and to clarify the question of stromal invasion. Wherever indicated, as in the case of a Class III or IV smear or carcinoma in situ diagnosed by ring biopsy, a wide cone of cervical tissue should be removed in the postpartum period to establish the definitive diagnosis and treatment.

We have found that the cytoplasmic content within the cells of the various layers of the epithelium which is stainable with the periodic-acid Schiff stain affords an objective method of determining the extent of epithelial maturation and metaplasia (4). An increase in positive staining material is noted in the epithelia of the cervix during pregnancy, but the basal cells of the ectocervix and reserve cells of the endocervix remain unstained. In fact, there is a sharp line of demarcation between the basilar cells and the more superficial cell layers. In the cases of marked basal cell hyperactivity, only the most superficial cells are positively stained, and in carcinoma in situ the entire thickness of the epithelium is made up of basal or reserve cells that contain no PAS stainable material. The surface and alveolar columnar epithelia of the endocervix take a heavy stain; however, hyperplastic or anaplastic reserve cells remain unstained (Fig. 1). Thus, one can distinguish between normal columnar epithelium or squamous metaplasia of the mature type and hyperplastic or carcinomatous lesions of the endocervix. Moreover, in the latter cases hyperplastic lesions are distinguishable from carcinoma in situ because some degree of cell maturation will be present and the matured cells will be PAS stainable. It appears, therefore, that carcinoma in situ is a distinct entity characterized by complete failure of cell maturation. In the endocervix there is complete lack of cell differentiation as well as lack of maturation.

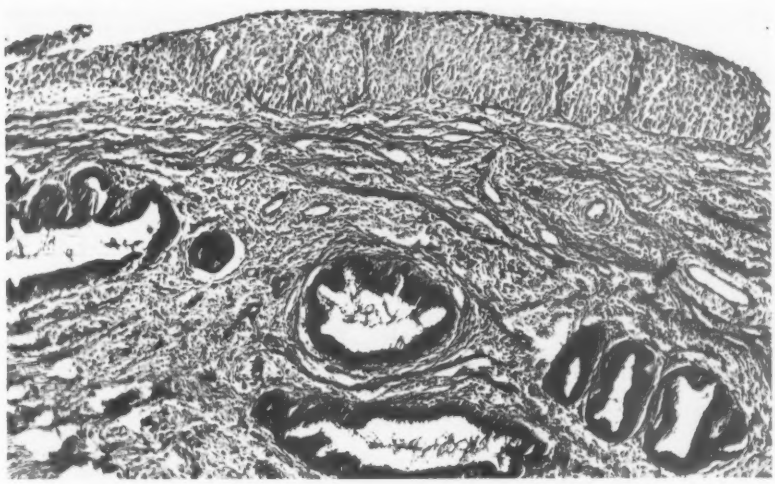

Fig. 1. Carcinoma in situ. Entire thickness of surface epithelium is made up of unstained basal cells sharply contrasted with heavy PAS staining of the mature columnar endocervical cells, PAS, 130 X. From Nesbitt and Stein (3).

It should be pointed out that the cervices with typical areas of carcinoma in situ of the basal cell type frequently show variations in the morphologic and staining patterns in contiguous areas of cervical epithelium. One of the histological varients takes the form of atypical hyperplasia with delayed or irregular maturation in the mid-zonal layer (Prickle cell hyperplasia). Recently, we have suspected this lesion in two non-pregnant patients who demonstrated in their vaginal smears a high degree of cellular atypism of the navicular cell layer. In both instances, the presence of a prickle cell cervical lesion was proven by tissue studies. The epithelium was altered by the development of large, deep, club-shaped epithelial pegs throughout the basal zone with a marked cellular atypism of the prickle cell layer. The surface cells were irregularly differentiated but there was a fairly normal appearing basal zone (Figure 2).

Until more is known of the fine correlation of structure and function, considerable effort should be exerted to establish precise and uniform histologic, as well as cytologic, criteria for the broad spectrum of dysplasia lesions of the cervix. We know little of the biological potential of these lesions, and until we

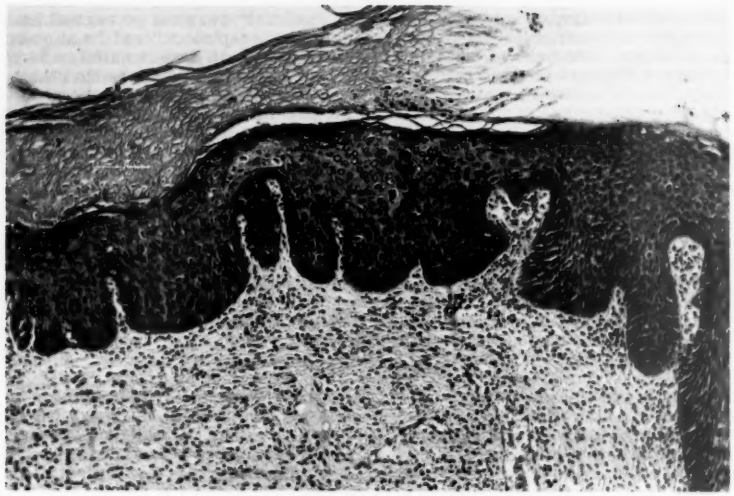

Fig. 2. Prickle cell hyperplasia. Note extreme cellular atypism of mid zone layer. Overlying superficial cells are normal. H & E stain, 130 X. From Nesbitt and Stein (3).

do, they should be subjected to every method of study available to us, including such techniques as cytochemistry, tissue culture, ultraviolet microscopy, colpomicroscopy, and, above all, prolonged follow-up without definitive treatment unless carcinoma is proven.

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GUILLERMO TERZANO

Buenos Aires, Argentina

The cervix of the uterus undergoes changes during pregnancy (6, 14, 16): (a) in the stroma: congestion, inflammation and decidual reaction, (4, 15), (b) in the endocervix: glandular hyperplasia and epidermization (2, 4, 5, 11) and (c) in the extocervix: thickening of the epithelium with partial hyperplasia of the basalis (1, 2, 4, 7, 9, 10, 11).

Vaginal aspirations and cervical scrapings have been obtained from 470 pregnant women, and the following was observed:

Vaginal and Cervical Smears				
	Class I	Class II	Class III	Class IV
Normal Cervix	166	151	19	1
Pathologic Cervix	57	67	9	-
Total:	223	218	28	1
Percentages	47.5%	46.4%	5.9%	0.21%

In this series, 247 pregnant women (52.5%) have shown abnormal cells in their smears. Of these: 218 (46.4%) smears were classified as Class II, 28 (5.9%) as III (suspicious), and one (0.21%) as Class IV (false-positive).

Of the 218 cases classified as Class II (abnormal cytology with non-suspicious signs of malignancy the abnormal cells were derived from the ectocervix in only seventy of them.

The number of cases with actual abnormal cytology which includes them in the group of cervical dyskaryosis (29 or 6.1%) is relatively smaller in our series, compared with those given by others (3, 8, 11, 12, 17).

It was possible after delivery to study the cytology of 56 of the 218 women whose smears were reported as Class II, 19 of the age 28 cases reported as Class III, and one case reported as Class IV. All of them had Class I smears between the fourth and the eighth week after delivery.

The abnormal smears of pregnant women in our series became normal after delivery. Dysplasia during pregnancy would seem to be a reversible lesion, since it returns to normal after delivery. Cytological features in our cases were similar to those observed after diathermocoagulation of the cervix, endocervical biopsies or high estrogenic therapy.

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DISCUSSION

GEORGE J. ANDROS, Philadelphia, Pennsylvania, U.S.A.:

The definition of dysplasia must be clarified. If one uses this term to designate the histologic entity wherein there is proliferation of atypical "deep" cells into the more superficial epithelial layers but where the loss of the normal maturation pattern is less in degree than that associated with carcinoma in situ, then there will be no significant difference in the cytologic features of this condition in pregnancy as compared with the non-pregnant state.

Drs. von Haam and Nesbitt have presented this problem thoroughly. Dyskaryosis of some degree will be noted. If the cells seen are at all suspicious of carcinoma in situ, we feel that the cytologist is being presumptive if he does not have his findings correlated with adequate histologic study. In our clinic this implies coldknife conization biopsy during pregnancy.

JEAN A. de BRUX, Paris, France:

From my experience on dysplasias and on the so-called "carcinomas in situ" during pregnancy, I may conclude that in the present state of our knowledge, a dysplasia - even an apparently suspicious one - is certainly benign. A so-called "intra-epithelial carcinoma" must be considered with great caution as to its malignancy. A great number of such lesions heal spontaneously and completely a few weeks after delivery, as has already been observed by numerous other authors.

It is likely that these dysplastic lesions during pregnancy occur in relation to an excessive and probably unbalanced hormone level. It is here that we must seek the causes of the abnormal re-epidermizations of the ectropions, which are the major factor in dysplasias during pregnancy. In this connection, we found a hydatiform mole in a patient in whom the smears showed a concomitant cervical cancer. Eight weeks after curettage the cellular pictures improved progressively and finally were no longer those of a carcinoma in situ, but only of an atypical dysplasia.

JORGE CAMPOS R. de C., Lima, Peru:

During pregnancy, especially during the last months, the cervical epithelium frequently shows changes in its normal structure, due fundamentally to greater proliferative activity of the basal cells. This cervical dysplasia does not have a definite histological pattern; it may show various pictures, even those of carcinoma in situ.

This histological alteration has its peculiar cytological expression in the cervical smears. Increase in number and size of parabasal cells, cytoplasmatic vacuolization, opaque nuclei, sometimes binucleated cells and definite atypical nuclei are frequent findings in cervical dysplasia of pregnancy but are not characteristic. Navicular cells, when present, allow differentiating the above-mentioned dysplasia from dysplasias of different etiology.

As established by Nesbitt and co-workers, with experience it is sometimes possible to differentiate cellular atypias due to benign conditions from those associated with malignant processes. It is, however, not safe to make a diagnosis by cytological means alone. Final diagnosis should be made histologically.

A pending problem is the evolution of the cervical dysplasia of pregnancy after delivery. There is a considerable discrepancy of opinion among the authors. Our experience (1) shows that the cervical epithelium recovers its normal structure between six and twelve weeks post partum, but this observation is based on a relatively small series of cases studied during a short period of time. It is possible that by studying a larger series and by studying the development through several pregnancies, it would be possible to learn the real significance of cervical dysplasia of pregnancy and its relation to carcinoma of the cervix, if any exists.

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CAMILLE LICHTFUS, Athus, Belgium:

We have studied over 1,000 pregnant women near term, not only to determine the duration of the pregnancy, but also to discover cervical lesions.

In 185 cases we found infections caused mostly by Trichomonas vaginalis. In 20 cases without infection, the smears were classified as Class II of Papanicolaou; only two cases were Class III.

In these 22 cases, colposcopy was done simultaneously with cytology. We followed all these women by means of vaginal smears and colposcopy over a period of six months to three years after delivery. Twenty-one were negative.

One case in the Class III classification continued to be a Class III eight months after delivery. A conization was done and the histology showed only a large leukoplakia without cancer.

We also belive that all cervical dysplasias discovered during pregnancy must be followed by smears, not only during pregnancy but also post partum, and proper biopsies should be done under colposcopic control.

DEAN L. MOYER and LOUIS J. ZELDIS, Los Angeles, California, U.S.A.:

The dysplasias occurring during pregnancy are characterized chiefly by abnormalities in differentiation, of which the most striking feature is nuclear immaturity, as pointed out by von Haam. The cellular changes are basically similar in pregnant and non-pregnant women. This occurrence, as emphasized by Nesbitt and his group, no doubt reflects the similarity of the stimuli-hormonal, inflammatory, etc. - that occur in both pregnant and non-pregnant women, varying chiefly in magnitude. A correlation of the cytologic and histologic findings in a group of 34 pregnant women with smears suggestive of dysplasia (III) to us, indicate that when dysplastic changes are noted cytologically, there is an excellent probability that the lesion will be proven by careful histologic study.

The cytologic dysplasias in the pregnant women are commonly associated with a basal cell hyperplasia in the ectocervix and a reserve cell hyperplasia involving both the surface and gland linings of the endocervix. The cytologic findings characterizing basal cell hyperplasia have been well-described by others, including von Haam in his preceding discussion. The sizes and shapes of such cells approach those of normal superficial and navicular cells. The cell membranes are intact and the cytoplasm is usually green-blue, although occasionally the inner half surrounding the nucleus may be faintly tinted with yellow-orange. The relative immaturity is evidenced by the enlarged nucleus and slight hyperchromasia with finely divided chromatin granules.

The reserve cells, on the other hand, may be prominent in dysplastic smears, and in many patients outnumber the dysplastic basal cells. The exfoliative research cell shows more variation in size and shape, and although the majority are oval or ellipsoidal, rare forms are elongated. The cytoplasm is usually vacuolated with multiple droplets. The vacuoles are never markedly enlarged, as in histiocytes, to distend the intact cell membrane. The cytoplasm is green without eosinophilic areas. The nuclei more frequently show irregularities of shape and a coarser nuclear membrane than do basal or parabasal cells. The nuclei tend to be hyperchromatic and the chromatin coarsely distributed. Occasional nuclear wrinkles are present.

Continued studies of the type reported in this symposium are helpful in the more precise distinction between dysplasia and carcinoma of the cervix in cytological smears. While more definitive criteria would offer great assistance in the management of pregnant patients with abnormal cytology, we

would, with Nesbitt, emphasize that tissue examination should not be withheld in the presence of suspicious or malignant cells in the smear. Tissue should be adequate not only to resolve the presence or absence of malignancy, but to permit satisfactory evaluation of the presence or absence of invasion.

CLOSING REMARKS

EMMERICH von HAAM:

The differentiation of dysplastic basal cells and dysplastic reserve cells as proposed by Moyer and Zeldis is interesting and offers a new challenge to the cytologist. The important thing is to point out, in agreement with the other discussants, that cellular dysplasia in pregnancy does not represent any form of carcinoma in situ but is the result of disturbed hormonal balance and will regress in most cases after termination of the pregnancy.

ROBERT E. NESBITT, Jr.:

As we have employed the term in this report, "dysplasia" refers to that group of cervical lesions characterized by "atypical" epithelia which are abnormal but do not fulfill all the cytological or histological criteria required for a diagnosis of carcinoma. We are in agreement with Andros that there is no significant difference in the cytological or histological features of these lesions in pregnancy as compared with the non-pregnant state, but it is our impression that the incidence of such lesions is greater than in the latter group. It would appear that the increased incidence is due primarily to a greater number of these lesions found in the endocervix of pregnant women. More study is needed, however, before far-reaching conclusions are justified.

Our experience agrees with that of Campos in that a majority of these dysplastic lesions of the cervix are reversible and that a high percentage disappear by the sixth postpartum week. Serial biopsies during the antepartum and postpartum periods taken from 84 patients from our obstetrical clinic demonstrated that basal cell hyperactivity present during the course of pregnancy had an 85.7% chance of reverting to normal or to a lower grade by the sixth postpartum week. In a study of 38 patients who had basal cell hyperactivity demonstrated by cervical biopsy at the sixth week post partum, it was further demonstrated that 26.3% of the cases will still have the process in some degree at six months. In this small series there was no demonstrable tendency for regression to occur after that period of time; thus, the possible role of basal cell hyperactivity as an antecedent lesion in the life history of cancerous lesions of the cervix makes the postpartum follow-up of all cervical lesions in pregnancy mandatory, even though regression apparently occurs in the majority of cases. We have only limited data concerning the evolution of basal cell hyperactivity through several pregnancies. Nevertheless, based upon histological data from eighteen patients studied during at least two pregnancies, it would appear that the incidence of basal cell hyperactivity of the cervix in subsequent pregnancies corresponds to the grade of hyperactivity of the cervix in the initial pregnancy. The incidence of basal cell hyperactivity was 25% among patients who had had minimal hyperactive lesions of the cervix in the preceding pregnancy, as compared with a 60% incidence for those cases showing Grades II or III hyperactivity initially. More work in this area of the problem should be rewarding.

The cytological technique should be regarded as an important screening test rather than a definitive examination for cervical cancer. Histological confirmation of doubtful or positive cytological findings is required before definitive diagnosis or treatment of a lesion is justified. The close correlation between the two techniques and the special value of the smear in detecting non-clinical lesions justify confidence in the smear technique alone as a screening device, when there is no "target" lesion to biopsy. The majority of advanced cases detected by the smear are readily diagnosed by the histological technique. When an easily recognizable, gross lesion is present in the cervix, it is only common sense to subject it to biopsy.

We are in agreement with Andros that, even during pregnancy, adequate cervical tissue must be removed in selected cases to properly evaluate markedly dysplastic lesions. We believe that the cervix of pregnant women demonstrating the histological criteria of carcinoma in situ on punch biopsy should be subjected to a wide ring biopsy or shallow cone biopsy for the purpose of excising the squamo-columnar junction and the adjacent gland-bearing area. These procedures are feasible without compromising the integrity of the internal os. Blood loss, which is marked only occasionally, can be readily controlled by suture or electrocoagulation at specific bleeding points. If no invasion is found, the pregnancy is allowed to continue to term and delivery provided meticulous follow-up of the patient is instituted with re-examination of the pelvis at intervals, cytological smears as indicated, and colposcopy, if available. It has been our custom to subject most of these patients to definitive diagnostic procedures at six weeks post partum, usually by a wide deep cervical conization, particularly if the smears continue to be abnormal. It is advisable to place all such patients, even those who are proved to be free of cancer by extensive study, in a specialized clinic designed for the prolonged follow-up of "suspicious" cases.

We were interested in de Brux's case in which there was regression in the cytological characteristics of a cervical lesion following evacuation of a hydatidiform mole. There is no doubt that epithelial morphological alterations do occur in response to exogenous or endogenous hormones. Basal or reserve cell hyperactivity of the cervix, even to a degree reminiscent of carcinoma in situ, has been observed in fetuses during the first several days of life, in certain elderly women, occasionally during pregnancy, in patients receiving intensive hormone therapy and in patients with stromal hyperplasia of the ovaries. It is likely

that the trigger mechanism can arise from a variety of stimuli, and only a few, such as conditions associated with excessive or unbalanced hormone levels, are discernible by our current techniques of study. Disappearance or apparent regression of such cervical lesions has been reported, particularly following pregnancy, by several authors, including ourselves. Nevertheless, the incidence of regression of carcinoma in situ lesions is unknown. It is assumed to be low if it truly occurs, and is, at best, an unpredictable occurrence. The possibility of regression should, in no way, mitigate the urgent need for adequate histological study, including sharp conization, of all such patients in the postpartum period. At the same time, however, it seems reasonable that one should abstain from definite therapy until the lesion has been demonstrated and thoroughly investigated in the non-pregnant state.

GUILLERMO TERZANO:

The presence of abnormal parabasal cells (dyskaryotic or not) in the vaginal and cervical smears of pregnant women usually means dysplasia. A close follow-up is recommended to indicate when a biopsy should be made.

In our series, all of the smears have become Class I, negative, after delivery. For this reason we cannot yet make a formal statement, apart from classifying the case as dysplasia of the cervix during pregnancy.

COMMENTS ARE INVITED
ABOUT ANY OF THE SUBJECTS TREATED
IN THE SYMPOSIA BY CORRESPONDENCE.

THE COMMENTS WILL BE PUBLISHED
IN THE SECTION "LETTERS TO THE EDITORS."

EXFOLIATIVE CYTOLOGY OF CARCINOMA IN SITU DURING PREGNANCY

JEAN A. de BRUX AND JACQUELINE DUPRÉ-FROMENT
Paris, France

The problem of carcinoma in situ is intrinsically very complex, and its coexistence with pregnancy only increases the difficulty. A study of this situation, therefore, can only be conceived in relation to an ensemble of other lesions; hence, the cytology of the carcinoma in situ will be compared with the dyskaryoses and with the regular and irregular dysplasias.

Schematically, the epithelial anomalies observed during pregnancy are manifested on smears by three types of nuclei:

(a) dyskaryotic nucleus
(b) dysplastic nucleus
(c) intra-epithelial carcinomatous nucleus

(a) The dyskaryotic nucleus is an incompletely mature nucleus situated in an immature, cyanophilic cytoplasm. It is born of an element too florid in the beginning, the maturation of which is only roughly sketched. Then follows an imperfect nuclear retraction and chromatin densification terminating in the characteristic morphological anomalies. All gradations may be found, from the voluminous regular nucleus with active, finely dotted chromatin to the pseudo-budding nucleus, more or less notched and roughly folded, and whose chromatin is of heterogeneous density, distributed in plaques of various shades oriented like the facets of a crystal. In spite of these alarming aspects, the absolute benignancy of such a cell may be affirmed in view of persistent fineness and brightness of the chromatin. The cytoplasm, always cyanophilic, often presents a faint, pale halo around the retracted nucleus (Figs. 1, 2).

(b) The dysplastic nucleus has two types:

(1) The one, resembling the nucleus of the dyskaryotic cell, at times somewhat denser and more contracted, is situated in an eosinophilic cytoplasm.

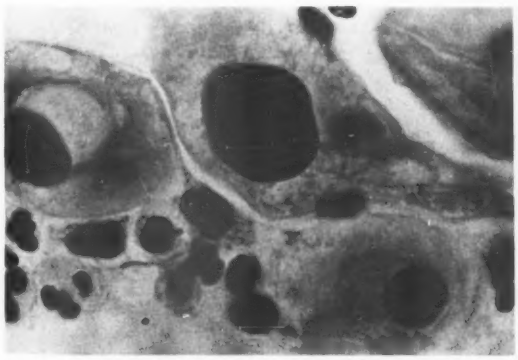


Fig. 1. Two dyskaryotic cells.

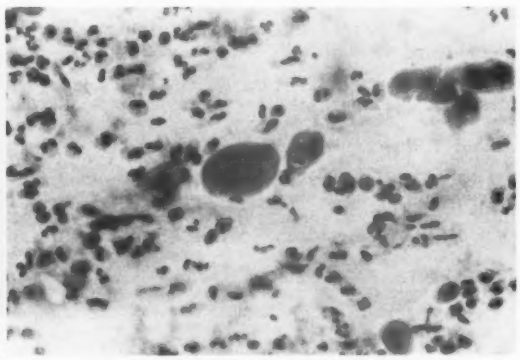


Fig. 2. Dyskaryotic cell with a lobulated nucleus.

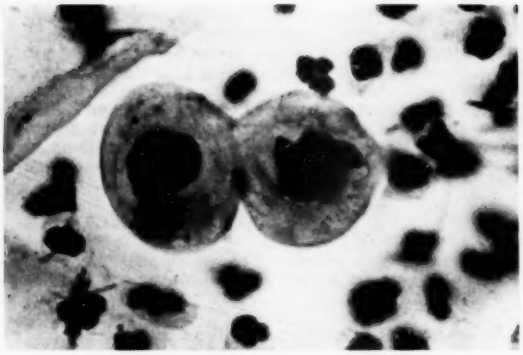


Fig. 3. Dyskaryotic cell with opaque chromatin and very irregular outline, slight perinuclear halo. The cytoplasm is eosinophilic.

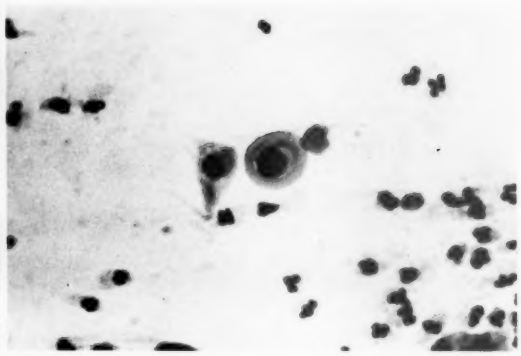


Fig. 4. Two dysplastic cells. The first is of inflammatory type and the second is a true dysplastic cell with a perinuclear halo.

(2) The other, a dysplastic nucleus in the true sense, testifies to a malformation, either originally or later as a result of a disturbance in the mechanism of its maturation (Figs. 3, 4).

Like that of the dyskaryosis, the dysplastic nucleus, although to a less marked degree, is polymorphous and often irregular, roughly round or elongated, with distinct outline, often notched and angular, and is always voluminous. But, in contrast to the dyskaryotic nucleus, its chromatin is opaque, and the design, as well as the nucleolus, is invisible. It spreads in dense, dark sheets, or may even have the appearance of a compact, inky-black mass, without discernible nuclear membrane.

The cytoplasm may remain cyanophilic, and in this case may show a light perinuclear halo of retraction, much more accentuated than in the dyskaryoses. Or the cytoplasm may cornify and often turn orange, with the perinuclear halo faded or barely traced.

These different aspects give evidence of a discrepancy in maturation between nucleus and cytoplasm. One may, therefore, find two extreme forms: either cells with precociously cornified cytoplasm, and nucleus in process of maturation, or cells whose nuclei have abruptly matured, in a still immature cytoplasm.

(c) The intra-epithelial carcinomatous nucleus is young, more compact than chromatic, situated in a cytoplasm which is always cyanophilic, and conforms with nearly all the criteria of malignancy. The nuclear-cytoplasmic ratio is reversed, the nuclear membrane is thickened, the nucleolus is enlarged and sometimes multiple, the chromatin is lumpy and irregular, and the mitoses are numerous, often abnormal and multipolar. Nevertheless, the nuclear outlines are strikingly distinct and barely notched. Surrounded by a more or less large cytoplasm, it resembles a parabasal cell. Its only distinguishing features are the anomalies of its chromatin, which is always visible, dense and active, grainy or on the contrary broken into large, unequal blocks, sometimes disposed along the nuclear membrane around a central vacuole (Fig. 5).

Governed by the same laws of maturation as the other nuclei, it is likely to become modified during its rise to the surface of the epithelium. On retracting, it may become irregular, with festooning of its outlines and folds in its mass, even while conserving its characteristic chromatin. In extreme cases, it densifies into a block and assumes the aspect of the dysplastic nucleus (Fig. 6).

Once the cellular anomalies encountered during pregnancy have been defined, they must be put back into their histological context, and their aspects on the smears demonstrated:

The aspects of the lesion have been described under the headings of histology, dyskaryosis, the regular dysplasias, the irregular dysplasias, the "carcinoma in situ-like," and the true carcinoma in situ.

The smear of dyskaryoses

The dyskaryotic squamous epithelium conserves perfectly harmonious architecture and is abnormal solely by its constituent cells: This abnormality is evidenced on the smear by an ensemble of elements of basal and intermediate type, all or nearly all of them cyanophilic, but the polymorphous nuclei of which range in form from round and regular with active chromatin, to pseudo-budding (Fig. 7).

The smear of dysplasias

On the histological side, two types of dysplasias can be defined:

The regular dysplasia: architecture normal, cellular morphology abnormal but of strictly dysplastic type.

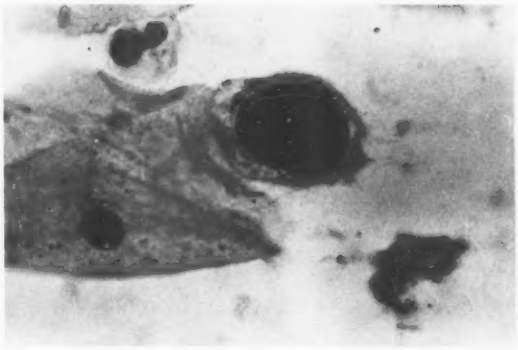


Fig. 5. Cell from a carcinoma in situ.

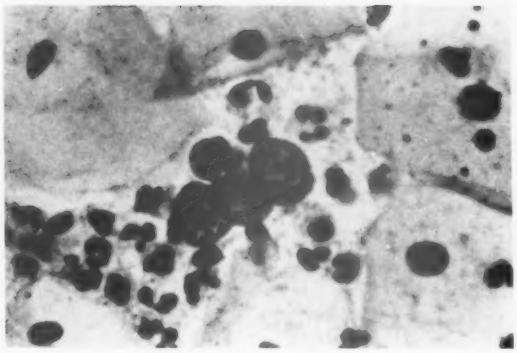


Fig. 6. Naked nuclei from carcinoma in situ.

The irregular dysplasia: disturbed architecture, some of the constituent elements being of dysplastic type, others being of intra-epithelial carcinomatous type.

The cytological translation of these architectural concepts on which the histologist bases his diagnosis are not found on the corresponding smears. Nevertheless, from the appearance of a smear, we may often determine the regular or irregular character of the lesion.

From the outset, the dysplastic smear, whatever its type, is striking by its polymorphism and the abundance of mature elements with cornified cytoplasm.

If the dysplasia is still regular, one observes elements of parabasal and intermediate type, of variable form: round or elongated, resembling a fiber or a tadpole; their nuclei, of dyskaryotic aspect, are more or less mature (Fig. 8).

When the dysplasia is irregular, the same cytoplasmic deformations are found, but the nuclear anomalies are aggravated and are of dysplastic type. In addition, there exist, in smaller number, immature parabasal cells strictly resembling those of carconoma in situ, i.e., regular in form but with malignant chromatin.

The smear of carcinoma in situ

This is composed of the same elements as the irregular dysplasia, the nuclei being of dysplastic and of intra-epithelial carcinomatous types, the proportions of each being reversed.

In those we have called "carcinoma in situ-like," the number of the dysplastic elements and the eosinophilia are still marked (Fig. 9): in the true carcinoma in situ, their number decreases to the point where all or almost all cellular elements are composed of immature carcinomatous cells (Fig. 10).

Whereas a trained eye is capable of distinguishing without hesitation the dyskaryotic elements in a smear of pregnancy, such as the cells of a regular dysplasia, the problem becomes very difficult when one confronts the irregular dysplasias and the carcinoma in situ.

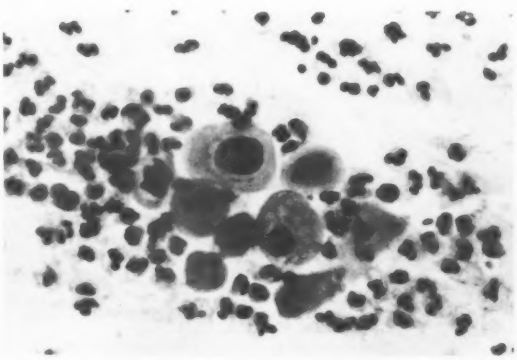


Fig. 7. Smear from dyskaryotic squamous epithelium.

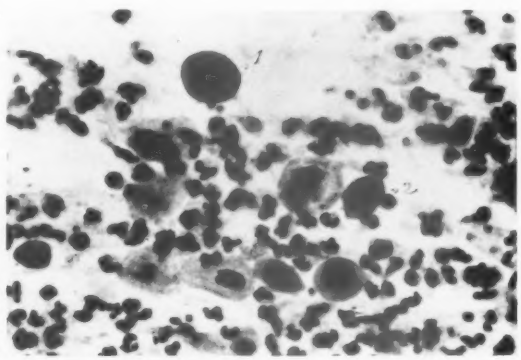


Fig. 8. Dysplasia: Note the mixture of dysplastic (1, 2, 3,) and dyskaryotic cells.

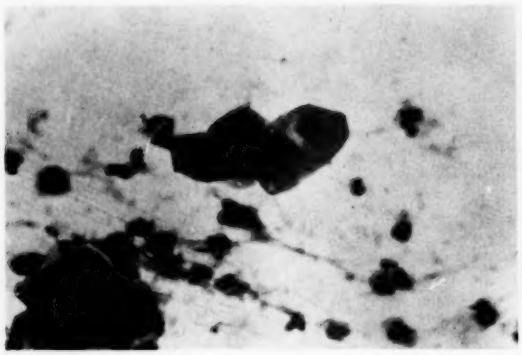


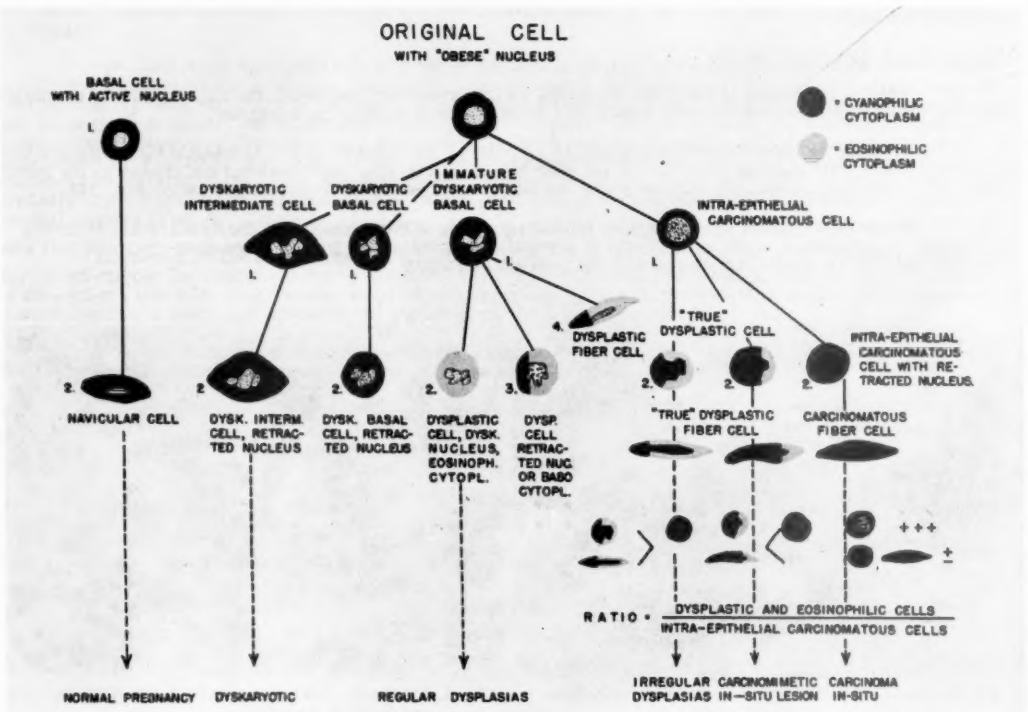
Fig. 9. Cluster of cells exfoliated from a "carcinoma in situ-like" dysplasia, with perinuclear halo in a very cyanophilic cytoplasm.

Fig. 10. Two cells from a carcinoma in situ and a naked nucleus.

In order to determine the lesions precisely, it is necessary to determine the level of the abnormal dysplastic cells in relation to that of the cells of carcinomatous type, and to establish their ratio. Thus, for very grave epithelial lesions the regression of which has been observed after parturition, we have been led to adopt the term "carcinoma in situ-like," which we consider the most severe form of the benign dysplasias (borderline) (Fig. 11).

SUMMARY

It is very difficult to determine with absolute certainty the abnormal elements exfoliated from the cervical lesions of pregnant women. Nevertheless, we have a more exact approach to the problem when bearing in mind the cellular anomalies inherent in the gravid state. A recognition of the entity "carcinoma in situ-like" should inspire an extreme prudence in the choice of therapy.



GENEVIEVE DALIAN, ARLETTE SIMATOS AND VIOLETTE M. NUOVO
Paris, France

CYTOLOGY

It is our experience that in vaginal smears, the cytological criteria of a carcinoma in situ include superficial intermediate cells and parabasal cells invariably presenting a well-preserved cytoplasm and enlarged, somewhat irregular, non-homogeneous, often hyperchromatic nuclei (these are also more or less the criteria of a dysplasia), and the presence of groups of undifferentiated cells with very large, irregular, often clear nuclei. It is the authors' opinion that on this type of smear one should not observe monstrosities or strangely-shaped cells such as tadpole cells, fusiform cells, etc.

This description of the cytology of carcinoma in situ is common to both the pregnant and the non-pregnant patient.

RESULTS

Among the 26 cases of carcinoma in situ found during pregnancy in our study, three distinct types were apparent. All of these cases have been rescreened:

1. Three cases (Class III) appeared to be cases of dysplasia. The abnormal cells were all differentiated with light alteration of the nuclei.
2. Nineteen cases had smears showing all the cytological criteria of a carcinoma in situ as described previously.
3. Four cases typified invasive carcinoma, cells with altered cytoplasm, marked atypia of the nuclei and fibroid cells.

CONCLUSION

The cytological diagnosis of carcinoma in situ seemed obvious in 19 out of 26 cases. This represents 73%.

It is interesting to observe the follow-up of the four cases which seemed cases of invasive carcinoma on the cytological examination:

1 was not followed.
1 had a conization and has been followed by means of smears which have remained highly suspicious during a period of two years.
1 had an amputation of the cervix. The smears were still highly suspicious four months later. She then had radium therapy and the smears became negative.
1 has not received any treatment to this date and has had highly suspicious smears for two years.

One might wonder if these cases were not, in fact, invasive carcinoma.

COMPARISON WITH THE RESULTS OBTAINED IN CARCINOMA IN SITU ON NON-PREGNANT WOMEN

Among the 131 cases of carcinoma in situ in non-pregnant women, the cytological results were as follows:

2 were false negatives.
9 cases had a cytological appearance of dysplasia.
74 cases had typical carcinoma in situ smears.
46 cases had smears which seemed evident for invasive carcinoma:

10 had biopsies:
6 were not followed.
4 were followed by means of vaginal smears which remained Class IV.
3 had biopsies followed by hysterectomy with negative operative specimens.
33 had conization, amputation or hysterectomy which were positive.

So, in ten cases the final diagnosis is uncertain since they only had a biopsy with no further treatment and no smears, or positive smears. In 56% of these cases, the cytological diagnosis of carcinoma in situ was obvious.

In conclusion, we again confirm our impression that the results obtained on pregnant and non-pregnant women are comparable.

This work has been done with the financial aid of the "Caisse Primaire Centrale de Sécurité Sociale de la Région Parisienne."

HERBERT E. NIEBURGS
New York, New York, U.S.A.

Exfoliated or abraded cells from the squamo-columnar junction of the cervix usually retain the morphologic characteristics of cells of the normal or malignant tissue at this site. Therefore, the diagnosis of cervical lesions by exfoliated cells depends on the individual approach of the pathologist to the interpretation of tissue changes. If the benign, epithelial alterations commonly found during pregnancy, such as hyperplasia of the glandular elements, squamous metaplasia and basal cell proliferation, are well understood, and if knowledge has been acquired on the identification of exfoliated cells of such epithelia, the diagnosis of carcinoma in situ is made according to the same criteria as applied in non-pregnant women.

A diagnosis of carcinoma in situ, whether during pregnancy or in the non-pregnant state, is made in cytologic specimens according to general criteria such as anisokaryosis, increased nuclear-cytoplasmic ratio, hyperchromasia, etc., subject to the fact that the typical malignant cells of invasive cervical carcinoma, such as giant cells and multinucleated cells, tadpole cells, and large nucleoli or karyosomes, are not present. Whether or not a diagnosis of carcinoma in situ by cytologic criteria is permissible in the presence of changes limited to the superficial and intermediate cell types, or if in addition also the cells of parabasal origin should present the characteristic atypical cellular alterations, depends on the standards adopted for the same diagnosis in tissue sections. In the writer's opinion, no diagnosis of carcinoma in situ should be made either in the non-pregnant state or during pregnancy, unless the characteristic atypical changes are also present in cells of the parabasal type and unless a certain degree of hyperchromasia in these cells can be noted.

Based upon long term observation of patients, it appears that lesions which were diagnosed as "carcinoma in situ" by less rigorous requirements have a questionable prognosis as to their invasive potential.

DISCUSSION

ANTHONY F. ANDERSON, Edinburgh, Scotland, U.K.:

Believing as I do that carcinoma in situ is a histological diagnosis and not justifiably a cytological one, I had hoped for instruction. I find, however, impressions from Paris so subjective as to be unacceptable and favour Nieburg's remarks as the most enlightening. I should like to hear more of our pundits say they believe carcinoma in situ is the same lesion whether the patient be pregnant or not, and I think we are making too heavy weather of the description of in situ cells. We either believe in these or we don't.

The figures of Dalian et al encourage me in my belief that trying to be a "cytological tipster" is a waste of time, with 74 cases correct and 46 "over-reported," and may be even a danger to the patient, if the clinician does not understand which part of the cytology report should be given full weight and which left for histological confirmation.

GEORGE J. ANDROS, Philadelphia, Pennsylvania, U.S.A.:

I agree entirely with the statements of Nieburgs. The criteria for a cytologic "diagnosis" of carcinoma in situ during pregnancy are the same as in the non-pregnant state. Maximal effort, in the form of cold-knife conization biopsy during pregnancy, should be made to rule out invasive malignancy.

J. ERNEST AYRE, Miami, Florida, U.S.A.:

Cervical cell scrapings from known carcinoma in situ lesions followed throughout pregnancy will frequently show an accentuation of cell pathology as pregnancy progresses. However, we have not observed or have been able to detect evidence of progression to invasive cancer during pregnancy. Those cases showing alarming cell progression during pregnancy may be safely subjected to ring biopsy excision without danger of abortion. The infiltration of cervical tissues with dilute novocain and adrenalin provides the operator with a bloodless operative field even though surgical procedures during pregnancy with general anesthesia are usually associated with active bleeding and hemorrhage.

Basically, the cytology of carcinoma in situ is the same during pregnancy as in the non-pregnant state. It is particularly noteworthy that a high Karyopyknotic Index, a rare finding in normal pregnancy, is almost invariably manifested in cell scrapings from the pregnant cervix which harbors carcinoma in situ or genuine premalignant lesions.

Dr. Kamnitzer has made an excellent and very intensive study of cytological manifestations during pregnancy and the postpartum period. His interesting findings warrant careful study.

From the standpoint of cancer detection in medical practice, it would seem wise to recommend that all women have routine cervical cytology as part of their final postpartum examination.

JACQUES W. JENNY and ALFRED WACEK, Zürich, Switzerland:

Usually the smears in pregnancy contain abundant material, also very often many leukocytes, histiocytes and mucus. Marked inflammatory reactions, however, are relatively rare. The nuclei are voluminous without change of the nuclear-cytoplasmic ratio. The chromatin structure is fine. Autolytic and especially cytolytic changes are observed in a large number of cases. This, together with the special type of desquamation during pregnancy, can render the differentiation of the smears more difficult. It is therefore possible that on routine examination slight pathological changes and even atypical cells, if occurring only in small numbers, may be missed. On a second examination, with special attention towards early pathological changes, they are likely to be found. The following table shows our results. (Series of 500 pregnant women, plus all cases of carcinoma in situ and invasive cancer of the cervix found in pregnant women during the years 1951-1957):

Routine examination		Second examination		Histology
smear		smear		
positive	negative	positive	negative	
7	1	8		Cervical carcinoma Stage I
7	3	10		Atypical epithelium
2	4	5	1	Dysplasias ("Unruhiges Epithel")
1	4	1	4	Basal cell hyperactivity, BCH I (and II)
8	6	13	1	Normal

The reading of the smear in pregnancy follows the same criteria as in non-pregnant women. According to Nieburgs, the suspicion of a carcinoma in situ should only be made, if the characteristic atypical changes are found also in parabasal and basal cells and if there is some degree of hyperchromasia. In our experience, this is true. However, this criterion applies not only to the carcinoma in situ (and invasive carcinoma), but also to a large number (about 50%) of cases with dysplastic ("unruhiges") epithelium. It does not apply to basal cell hyperactivity and the false positive smears.

We followed the classification of Papanicolaou. We do not think that a further differentiation of the cytological pictures into dyskaryotic, dysplastic and "carcinoma in situ-like" types has any practical value. A positive or a repeatedly suspicious smear must in any case lead to further examinations (i.e., colposcopy including surface biopsy (Schiller), possibly cone biopsy), since in our opinion a definite diagnosis on the sole basis of a vaginal smear is impossible and not permissible.

CLOSING REMARKS

HERBERT E. NIEBURGS:

I have read with interest Ayre's statement, "cervical cell scrapings from known carcinoma in situ lesions followed throughout pregnancy will frequently show an accentuation of cell pathology as pregnancy progresses." Possibly, further elaboration of this point by Ayre in one of the future issues of Acta Cytologica may add to the understanding of carcinoma in situ under the influence of the metabolic circumstances prevailing during pregnancy. In my material, cytologic changes without progressive histologic alterations could not be observed. However, I regret that I do not quite understand what Ayre means by "accentuation of cell pathology." In addition, the specimens examined were obtained by the cotton-tipped applicator and not by cell scrapings.

I am very glad to find that Drs. Anderson and Andros agree with my findings.

I find it difficult to understand the statement made by Drs. Jenny and Wacek, that parabasal cell hyperactivity with hyperchromasia also occurs in about 50% of cases with epithelial dysplasia. This is contrary to my findings in cytologic specimens as well as in histologic sections.

VIOLETTE M. NUOVO:

We wish to comment only on the discussion of Anderson. The fact that cytology can make a definite diagnosis of carcinoma in situ in only 60 to 75 per cent of the cases does not seem so important to my point of view, though it is rather interesting to be able to give such an indication to the clinician. But, the fact that in our records 155 (26 pregnant women and 129 nonpregnant women) patients have had a diagnosis of carcinoma in situ made and histologically confirmed, only due to a positive routine cytological test, is very encouraging.

Moreover, I think it is normal when one devotes all ones time to a discipline, whether it is cytology or anything else, to try to improve its technique and to try to find more subtle criteria. On the other hand, I do not think there is danger for the patient, for in the case of positive cytology most of the cytologists suggest that it might be an invasive carcinoma or that it might be a carcinoma in situ.

However, cytologists always ask for histological confirmation.

EXFOLIATIVE CYTOLOGY OF INVASIVE CARCINOMA DURING PREGNANCY

EMMERICH von HAAM
Columbus, Ohio, U.S.A.

Since 1950, we have had the opportunity to study 22 cases of invasive carcinoma in pregnant women. Seventeen cases belonged to the clinical Stage I, five cases to the clinical Stage II. Thirteen lesions were suspected of being malignant by the symptomatology and the gross appearance of the cervix. In nine cases the diagnosis was first made by the routine cytological examination. The ages of the patients varied from 25 to 42, and all but three belonged to the Caucasian race. All were multiparous and most of them had large families.

The diagnosis was made in all instances by cytological examinations and confirmed by biopsy. Twelve cases were diagnosed as Papanicolaou Class III, eight as Papanicolaou Class IV and two as

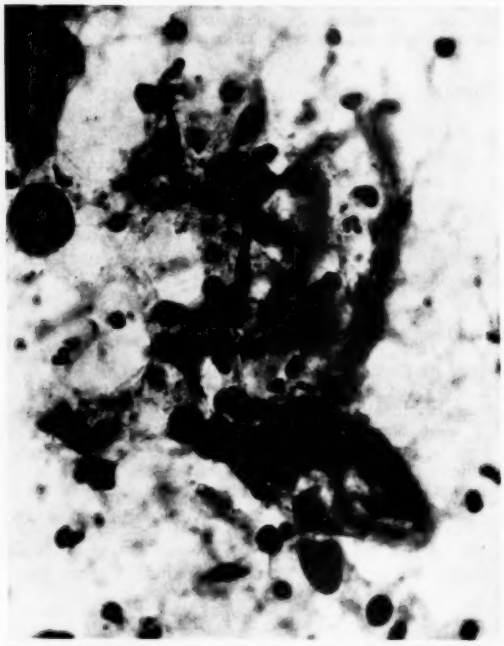


Fig. 1. Undifferentiated malignant cells in the smear from a carcinoma of the cervix, Grade IV, Stage I, of a woman in the fourth month of pregnancy. (X450)

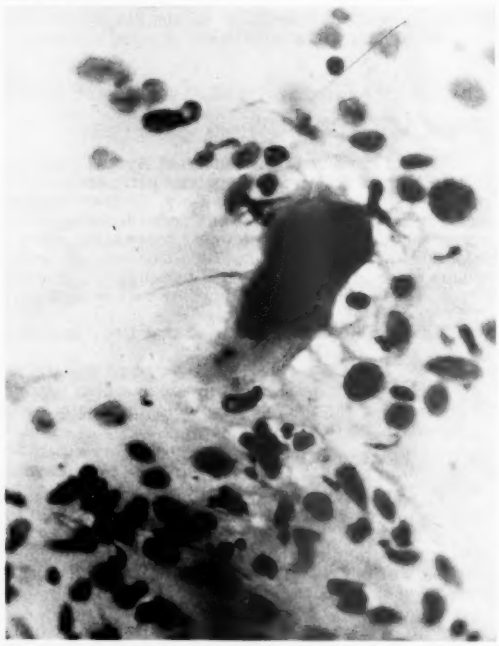


Fig. 2. Keratinized eosinophilic, malignant giant cell in the smear from a carcinoma of the cervix, Grade II, Stage II, of a woman in the seventh month of pregnancy. (X450)

Papanicolaou Class V. All lesions proved to be squamous cell with three belonging to the more differentiated type (Grade I), fifteen to the less differentiated type (Grade II or III) and four to the undifferentiated type (Grade V). Most of the cases belonged to the group studied clinically by Holzaepfel and Ezell (1) of the Department of Gynecology and Obstetrics of the Ohio State University and published in August, 1958. Readers interested in the type of therapy used in these cases and its results are referred to their publication.

The exfoliative cytology of our cases of invasive carcinoma during pregnancy differed in no way from that of invasive carcinoma of non-gravid women. The malignant-appearing cells were quite numerous and outstanding, and all types, from the small undifferentiated ones to the highly eosinophilic giant cells, could be recognized (Figs. 1, 2). In addition, the smears showed many leukocytes and red blood cells. The typical navicular cells of pregnancy were usually in a minority, and there were many more cyanophilic, karyopyknotic and eosinophilic, karyopyknotic superficial squamous cells. There were also many immature intermediate cells and atypical but nonmalignant parabasal cells. The normal bacterial flora of the healthy pregnancy smears was usually replaced by a mixed flora. The differentiation between the exfoliative cytology of invasive and noninvasive carcinoma was attempted following the suggestion of Wied (2), who achieved an accuracy of 85% by evaluating the surroundings of the epithelial cells, the quantitative relationship of the various cell types, and the locality and degree of degeneration of the atypical cells. To our regret we must confess that we were unable to do so in the majority of cases.

In his review article on cervical cancer in pregnancy, Kistner and co-workers posed the question, "How does pregnancy influence the behavior of the disease?" From the standpoint of exfoliative cytology we are not able to detect such an influence.

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DISCUSSION

HANNS-WERNER BOSCHANN, West-Berlin, Germany:

I am in full agreement with von Haam's statements, especially that the exfoliative cytology of invasive carcinoma shows no difference between pregnant and non-pregnant patients (12 cases). At the present stage of our knowledge it is not possible to determine from cancer cells in a smear whether they originate from a pregnant or a non-pregnant patient.

Since Papanicolaou's classical observation, we know that one of the most typical criteria of cancer cells is their "deafness to hormonal influence."

JORGE CAMPOS R. de C., Lima, Peru:

Even though our experience is based on a smaller series of patients than the one of von Haam's, the findings are similar. From the purely cytological point of view there are few possibilities of differentiating cervical carcinoma in pregnant women and the same condition in non-pregnant women: according to our findings neoplastic cells are similar in both conditions. The non-malignant cells during pregnancy may exhibit a pattern which suggests to the cytologist the diagnosis of pregnancy, but this is not true in all cases.

CLOSING REMARKS

EMMERICH von HAAM:

I wish to thank Drs. Boschann and Campos for their discussions. Unfortunately the typical pregnancy smear is usually replaced by a smear showing evidence of marked inflammatory changes, and for this reason a diagnosis of pregnancy cannot even be made on the basis of navicular cells.

CLINICAL VIEWPOINTS WITH SPECIAL CONSIDERATION TO THERAPY AND TIME OF THERAPY FOR LESIONS OF THE UTERINE CERVIX DURING PREGNANCY

WERNER BICKENBACH AND HANS-JÜRGEN SOOST
Munich, Germany

I.

The therapy, like the diagnosis, of cervical carcinoma demands special consideration.

Positive cytological findings (Papanicolaou Class IV or V) in a lesion of the non-pregnant cervix requires conization of the cervix and a fractionated curettage of the uterine cavity and the endocervix. As a diagnostic measure conization is far superior to a simple biopsy. In our clinic, among 46 cases (1) in which histological examination of biopsied tissue showed atypical or markedly atypical epithelium (carcinoma in situ), 11 cases were proved to be "invasive carcinoma" by conization and subsequent serial sectioning of the material. Similar results are reported by other authors (2, 3).

In pregnant women usually only a simple biopsy can be done without endangering the pregnancy. This should be done with the aid of a colposcope.

If histology shows atypical or markedly atypical epithelium (carcinoma in situ), no immediate treatment is required. We know from the extensive investigation during the last few years (4,5,6) that changes, interpreted as atypical epithelium, occur fairly frequently during pregnancy without a true carcinoma developing later. On the other hand, these specimens may have been taken from the periphery of an invasive carcinoma.

In any case, these patients must remain under careful observation until the termination of pregnancy, when a definite diagnosis can be established. In atypical or markedly atypical epithelium (carcinoma in situ) without signs of invasion, conization alone constitutes adequate therapy. In any case, conization is an excellent method of preventative treatment for carcinoma.

II.

If an invasive cervical carcinoma is discovered during pregnancy, it is necessary to adopt immediate therapeutic measures. Besides the usual scheme of treatment it is necessary to consider the age of the pregnancy and the parents' desire to have the child. In general the principle applies also in cervical cancer: the earlier a carcinoma is treated the better the result.

Because of the steadily improving results of the combined radium-x-ray therapy, we have applied this method of treatment more and more in our cases of cervical carcinoma during the last few years. With 515 patients treated during 1952, we achieved a five years survival rate of 60.4% (Stage I - 83.8%, Stage II - 75.2%, Stage III - 46.3%, Stage IV - 0%) (7). The primary mortality rate in Stages I and II was 0%. Therefore, we perform surgery in cases of Stage I cervical carcinoma only under exceptional circumstances, i.e., when there are no reservations regarding the general, as well as the local, operability.

We feel that Wertheim's operation or a modification thereof is more readily indicated during pregnancy for two reasons: (a) the patients are usually young women in good general condition; (b) the local operability is favored by the laxity of the tissues. However, in cases of doubt, the operation should not be undertaken. From our material it is evident that the combined radium-x-ray treatment is as successful as the surgical treatment during the first months of pregnancy. We cannot say whether or not this also applies to the later months of pregnancy.

Up to the 16th week of pregnancy we proceed with radiation therapy as if the pregnancy does not exist. The radium is inserted in a plate which is applied to the cervix, this is followed by x-ray therapy and then (after expulsion of the fetus) by intra-uterine radium insertions. Fetal expulsion usually occurs two to four weeks after commencement of therapy and is spontaneous.

From the 28th week on, we attempt to maintain the pregnancy. Fractionated irradiation with small doses of radium is applied during pregnancy. Monelle-filtered radium appears to be most suitable because of its very intensive short-distance β-radiation, while the effect of the dangerous radiation on the child can be ignored because of the short time of exposure. As soon as the child is viable, caesarean section is performed, followed by either Wertheim operation with subsequent x-ray therapy, or Porro's supra-vaginal hysterectomy with subsequent radium-x-ray therapy. Which procedure will be the one of choice in operable cases remains to be seen and depends on future experience. In order to exclude the deleterious hormonal influence of the postpartum period, we attempt to maintain an artificial hormonal level simulating that of pregnancy, until the completion of radiation therapy.

The most difficult are decisions taken during the middle trimester of pregnancy. If the parents are not very desirous of having the child, the pregnancy should be terminated as soon as possible, since the prognosis probably becomes more unfavorable the longer the carcinoma exists during pregnancy. In general, we deliver the child by Caesarean section and then proceed as for a case in the third trimester of pregnancy.

Radiation therapy with the aim of producing a healthy child is possible only from the 6th month onwards, since it is impossible at an earlier stage of pregnancy to apply a sufficiently high radiation dose to the lesion without harming the fetus (8). A few cases are described in the literature, where a healthy child was delivered after a cervical carcinoma had been treated with radiation therapy. We had such a case 10 years ago (8). Nevertheless, greatest caution is urged in the use of radiation therapy on patients with intact pregnancy because of the possibility of genetic harm.

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JULES-ANDRÉ BRET AND F. J. COUPEZ

Paris, France

Since agreement is necessary between the different authors in regard to the treatment of clinically evident cancer and micro-carcinoma, we want to discuss here only the proceedings in the face of such lesions which range from simple epithelial atypia to carcinoma in situ.

Ectopy and simple epithelial atypias (Hinselmann I and II)

It seems to us that the treatment of benign lesions of the cervix as a measure for prevention of cancerous cervical lesions has not been stressed enough. However, colposcopy and cytology seem to demonstrate the frequency of lesions appearing during pregnancy and the possiblity of transient or definite aggravation of the tissue during this period.

Therefore, it seems necessary to us:

(1) to perform systematically anti-inflammatory treatment in every patient with cylindris ectropion or simple dysplasia. Infection plays a definite role in the formation of dysplastic scars of the ectropion of pregnancy. It is also a factor of initiation for dysplasias previously present, which are already stimulated by pregnancy hormones.

(2) to destroy every remaining post-pregnancy ectopy and every benign dysplasia sheet which persists more than three months post partum. After this period there is little chance that a lesion which is present will disappear, and therefore, it is advisable to destroy them in order to avoid aggravation. This destruction is performed by simple electro-coagulation and checked upon after six months.

Marked atypical epithelium (Hinselmann III and IV)

These lesions are much more frequent during than after pregnancy. They are usually detected by cytology and confirmed by colposcopy, while the guided biopsy reveals the grade of severity. An anti-inflammatory treatment is initiated during pregnancy. This includes observation of their development with aid of the three search methods, which determine the direction of their evolution. This will be known about three to four months after delivery, and one of the following possibilities may occur:

(1) Disappearance of the colposcopic and histologic lesion, smear class II. In this case absolute non-interference is recommended, but observe after one year.

(2) The colposcopic lesion persists but the histology reveals only a simple atypia and the cytology is class II: one should destroy the lesion by means of electro-coagulation or diathermis resection and observe after one year.

(3) The colposcopic lesion persists, and the histology discloses neither regression nor aggravation; the cytology in class III. In this case large destruction by diathermia under guidance by the Schiller test should be done. For follow-up, colposcopy and cytology should be performed every four months during the first year.

(4) Positive colposcopy, cytology class III or IV, histology showing transformation of the dysplasia into a carcinoma in situ. In this case the same treatment as used for carcinoma in situ arising after the beginning of the pregnancy is recommended.

The definite carcinoma in situ

If histologically confirmed, this lesion deserves a monthly review during pregnancy by means of colposcopy and cytological smears. In this case as in that of a more benign lesion, all inflammatory symptoms must be taken care of by local treatment during pregnancy in order to reduce the possible consequences. The radical therapy will not be done immediately after delivery. If there is no invasion to be afraid of, a delay of three to four months (covered by cytological, histological and colposcopical studies) seems necessary to us to allow the control of a probable self-regression, which we repeatedly have observed. Also, the kind of active interference (extent of surgery) may then be determined. By this date, provided the lesion keeps the features of a carcinoma in situ, our preference tends towards limited surgical intervention in order to (1) preserve the maternal functions and (2) at the same time minimize the chances of recurrence.

Accordingly, six times we have done high amputations of the cervix. This technique, representing the intermediate between too little and too much, has certain advantages for us:

It permits a large excision into the external portion of the cervix.

It includes the largest part of the cervical canal where certain lesions ascend after delivery.

Finally, it permits serial sections of the entire cervix in order to rule out invasion at any place.

For five of our patients the results have been excellent, and there were no recurrences detected after three, 11, 18, 19 or 20 months, under a regular colposcopic and cytological control schedule (check-ups every two or three months during the first year, every four to six months during the second year). The sixth patient, whose smear remained class III after cervical amputation, presented, four months later, a small colposcopic recurrence (field pattern) which was histologically diagnosed as a carcinoma in situ.

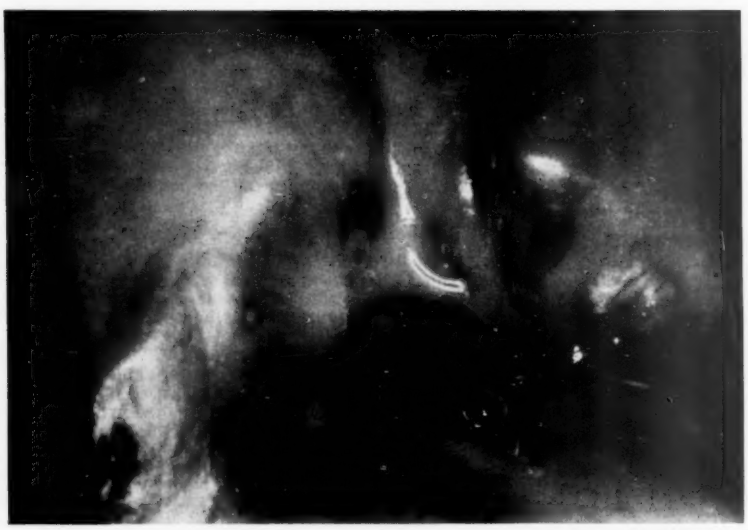

Fig. 1. MAT, 6/28/1957, new external os after amputation of the cervix, which has been treated six months after pregnancy for cytology class IV and histological carcinoma in situ. The cervix is shown six months after amputation. Smear class II, magnification 1.1 x, acetic acid.

Fig. 2. DUF, 2/18/1957, picture of colpitis of a new external os, after cervical amputation for class IV and carcinoma in situ. Six months after amputation, now class I, magnification 1.5 x, Lugol.

Because of certain difficulties in following her, she was treated with radiation therapy, and she has maintained, up to now, a cytological class II and normal colposcopy, 17 months after the first intervention.

Conclusion

If we exclude the fully progressed cancer, the micro-cancer and doubtful invasion, the best time for the treatment of cervical lesions seems to us to be the third to fourth month after delivery. By this time the cytological and histological survey usually has determined the direction of development.

All postpartal atypias of the cervix should be treated, including benign dysplastic scars and ectopies. The treatment should be as conservative as possible, ranging from simple electro-coagulation,

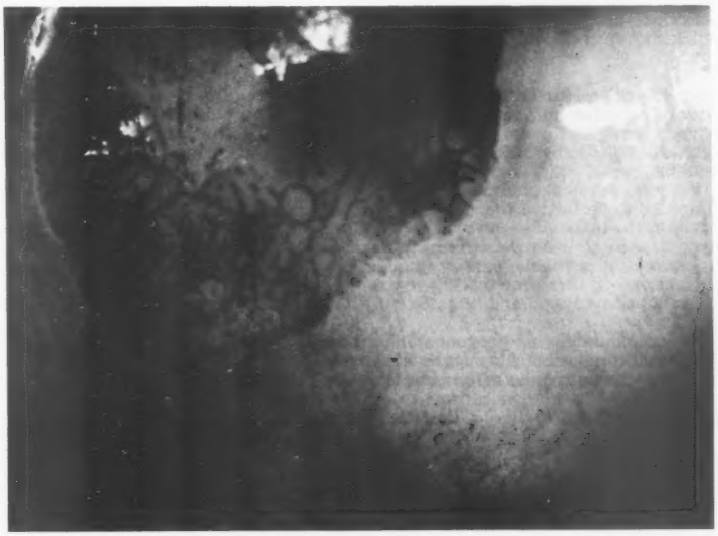

Fig. 3. OLJ, 2/4/1957, persistency of a class IV after amputation of the cervix for a carcinoma discovered during pregnancy. Field pattern. Histology discloses carcinoma. Magnification 2 x, acetic acid.

through local resection with the diathermic loop, to high amputation. This intervention must be followed-up by periodical cytological and colposcopical controls, the rhythm of which will be determined by the severity of the lesion.

Since infection appears to be a possible factor in the genesis of benign atypias and the transient aggravation of suspicious atypias, the local anti-inflammatory treatment of these disorders seems of very great importance in the treatment of the abnormal cervix during pregnancy.

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DISCUSSION

GEORGE J. ANDROS, Philadelphia, Pennsylvania, U.S.A.:

Proper care of the cervix during pregnancy should include, first of all, adequate cytological evaluation with cervical-endocervical smears. In addition, punch biopsies should be carried out as an office procedure in all visible areas which appear grossly malignant.

When cytology is not suspicious for malignancy and the lesion has the appearance of cervicitis, "erosion," ectropion, etc., medical treatment should be instituted during pregnancy. Gonococcal infection should be ruled out or treated until cultures are negative. Vigorous therapy should be insituted against trichomoniasis and candidiasis. After delivery, if cytology remains unsuspicious, local lesions should be eradicated with radial cauterization -- controlled by monthly examinations during the first half year after delivery and by cytologic study every six months. Occasionally conization of the cervix may be necessary as ultimate therapy.

A cytological examination that is in any way suspicious for malignancy should be affirmed promptly. In such cases cold-knife conization biopsy of the cervix should then be carried out during pregnancy, even though the cytology may point to in situ carcinoma.

We do not consider the presence of in situ carcinoma during pregnancy an indication for "emergency" therapeutic procedures, but we like to be quite certain that invasive malignancy is absent. Adequate conization biopsy with serial block histologic study of the specimen is the only practical means of achieving this reassurance during pregnancy.

In the last 1000 pregnant patients studied cytologically, we have performed cold-knife conization biopsies 12 times without interruption of the pregnancy. Two patients were found to have invasive malignancy, seven had carcinoma in situ and in three instances the histologic picture was that of marked anaplasia falling short of non-invasive malignancy.

When a definite diagnosis of carcinoma in situ has been made from conization biopsy, we follow the patient with cervical-endocervical smears at monthly intervals. Conceivably, the occasion may rarely arise when a cytological impression of invasive malignancy will be indication for repeat conization biopsy during pregnancy.

If the cytological picture after a conization biopsy revealing carcinoma in situ does not suggest a strong possibility of invasive malignancy, we allow the pregnancy to proceed to term. We have been performing caesarean sections for delivery in patients with a histologic diagnosis of carcinoma in situ during pregnancy in the Gynecologic Tumor Clinic of the Temple University Medical Center, but we realize that this is a debatable issue.

A decision as to definitive therapy in cases of carcinoma in situ diagnosed during pregnancy should be postponed until -- at least -- several weeks after delivery. Treatment then is carried out according to the individual case, depending upon the currently-determined histological findings (repeat conization) and upon the age, parity, etc., of the patient in question. We do not categorically forbid further pregnancy in every patient, nor do we proceed to hysterectomy at once in the postpartum period in young patients where subsequent cytologic and histologic follow-up fails to suggest residual carcinoma in situ.

Invasive carcinoma during pregnancy is, in our clinic, an indication for immediate definitive treatment of the cancer. Radiation or surgery is carried out in accordance with accepted principles. After the first trimester therapy is carried out after or concurrently with hysterotomy or caesarean section.

HANNS-WERNER BOSCHANN, West-Berlin, Germany:

Bret and Coupez give us precise rules for the treatment of lesions which are not yet invasive carcinoma. I should like to ask the authors if they would agree with the following:

Cylindrical ectropion is very common in pregnancy and very often disappears after delivery. Carcinoma in situ, which usually originates at the squamo-columnar junction, is more frequently seen

by colposcopy during pregnancy than in non-pregnant patients without apparently hormonally-caused ectropion because of the physiologic ectropion of the endocervix. However, if cytology is used, carcinoma in situ is diagnosed with the same frequency in both pregnant and non-pregnant women, since, in contrast to colposcopy, the endocervix is as easily reached as the ectocervix. For the same reason carcinoma in situ detected by colposcopy during pregnancy often seems to have disappeared after delivery if colposcopy is used again as criterion. The same lesion, however, if detected by cytology, persists after delivery, if cytology is used again as a criterion. Carcinoma in situ is sometimes combined with invasive carcinoma, e.g., as the preinvasive marginal area of an invasive carcinoma. On the other hand, neither colposcopy nor cytology are able to tell us with reliable certainty if a carcinoma is definitely not invasive. Considering this, I would prefer to perform a high amputation of the cervix if cytology indicates malignancy during the first months of pregnancy, avoiding the danger of having erroneously classified an invasive carcinoma as a carcinoma in situ. This operation, performed by a careful hand, does not disturb the pregnancy and, in the case of a carcinoma in situ, it can be considered as complete and definite therapy, as six years of observations of our material shows. During the last months of pregnancy, however, a series of cytological smears, collected under sterile conditions and perhaps assisted by colposcopy, can show the area from which the malignant cells are being shed. From that area a small biopsy should be obtained. If no signs of invasion are found and the smear appears to indicate the probable presence of a carcinoma in situ because of its predominant content of dyskaryotic cells, it should be permissable to wait one to three months after delivery and to perform the amputation of the cervix at that time. Colposcopically suspicious areas in pregnancy, however, can be observed without any surgical treatment, if repeated cytological controls which are collected at the suspicious area and screened by a trained cytologist reveal no evidence of malignancy. This does not exclude an anti-inflammatory treatment if necessary. I know that these important questions are still under discussion, and so I would be very glad to hear Bret and Coupez's opinion.

EDMUND SCHÜLLER, Vienna, Austria:

We take routine smears also in pregnancy. If we find a positive smear (Class IV or V), we carry out biopsies as in non-pregnant women. We have learned that cone biopsy in practically all cases does not harm pregnancy. Of course we cannot perform a curettage of the endocervix. This is not a disadvantage, because the squamo-columnar junction in pregnant women is moved towards the ectocervix (1), and we can be practically certain of removing the lesion with the cone biopsy.

If we find a dysplasia or carcinoma in situ on histological examination, no other treatment is required. After delivery we repeat smears for control. If an invasive carcinoma is discovered, we immediately perform a radical operation in the last trimester of pregnancy, in combination with classical caesarean section.

In the last two years we found four cases of cervical carcinoma in situ complicated with pregnancy. The cone biopsy did not cause abortion. In controls after delivery we obtained negative smears.

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CLOSING REMARKS

JULES-ANDRÉ BRET and F. J. COUPEZ:

In response to the opinions expressed and the questions asked by Schüller, Boschann and Andros, we must confess that we are not able to finally close the discussion. We want to explain a little more clearly, however, what elements have led us to our present attitude towards carcinoma in situ detected during pregnancy.

Boschann says that the colposcopic detection rate of carcinoma in situ during pregnancy is much higher than in non-pregnancy. We agree completely and explain this peculiarity in the same way as he does, by the better exposure of the squamo-columnar junction to visual observation. However, to us this does not appear to be the only reason.

Where cytological search is concerned we also found an increased detection rate during pregnancy when compared to after pregnancy and there is practically no discordance in the results of the two methods under consideration which we use jointly. The circumstances under which the systematic search is done (compulsory respective examinations for every pregnant woman, selective examinations for gynecological patients) stresses the validity of our statements. We conclude that the incidence of carcinoma in situ during pregnancy is much higher than outside of pregnancy, whatever the detection method employed. This conclusion obliges us to consider the problem of regressive changes and the resulting therapeutic consequences as a whole.

When we are faced with a cytological reading of Class 3, 4 or 5, which has been histologically classified as carcinoma in situ, our problem is twofold:

1. The diagnosis of beginning invasion should be made with great caution during pregnancy. Epidermal invaginations into the glands are an almost constant finding, and the glandular hyperplasia of pregnancy accentuates this aspect if the histological section is oriented in the right manner. We consider them, until more definite determinations are made, as being entirely capable of fooling the histologist, and we believe that true early invasion is very rare with regard to the number of carcinomas in situ found during pregnancy.

2. Several amputations of the uterine cervix done one to six months after delivery for a histologically characteristic carcinoma in situ have shown us very significant superficial regressions, as well as a lesser degree of a malignancy in the histological serial sections of the surgical speciman. These findings lead us to observe for a longer period our more recent patients before making a final therapeutic decision in spite of positive cytological findings during the first two months of the post-partum period.

At present we have three cases of complete cytological, colposcopical and histological regression under observation. One of these underwent an amputation of the cervix and the serial sections of the specimen did not show anything other than some dysplastic areas without any malignant characteristics. Therefore, we believe that in certain cases, lesions which histologically disclose features of a carcinoma in situ may well regress. The apparent malignant characteristics are only transient and are in some manner related to the conditions of pregnancy.

Schüller, Boschann and Andros who (in fear of overlooking an early invasion) practice early conization of the cervix, based merely on the cytological picture, seem to deprive themselves of a prognostic evaluation and the possibility of long term observation. The removal of the lesions which are the source of the positive cytological findings is probably the reason for their silence in regard to the question of a possible regression of these lesions.

We would like to have their opinion on this point. We will be glad to put colpophotographic, cytological and histological documentation at their disposal in case they are interested.

DIAGNOSTIC ACCURACY OF COLPOSCOPY AS COMPARED TO CYTOLOGY IN THE DETECTION OF CERVICAL CARCINOMA DURING PREGNANCY

FRIEDRICH BAJARDI
Graz, Austria

As we have already demonstrated in another publication (1), the diagnostic accuracy of colposcopy in the detection of preclinical cancer of the ectocervix is at least equal to the accuracy of cytology. Carcinomatous changes of the endocervix, however, will as a rule escape detection by colposcopy. In such cases cytology will show better results. Consequently the detection of early carcinomas, as far as colposcopy is concerned, depends on its localization, whereas cytology may be employed irrespective of such conditions.

It is a well-established fact that the starting-point of early carcinomatous changes of the cervix originates from the squamo - columnar junction. Depending on whether or not this place is located outside or inside the external os, either ectocervical or endocervical cancer will develop.

As recently demonstrated (2), during reproductive years the squamo - columnar junction is localized more often at the ectocervix. In elderly women, on the other hand, this junction very often is to be found in the endocervix.

Consequently, the diagnostic accuracy of colposcopy is expected to be higher in younger women, including pregnant women, as endocervical carcinomas are not to be anticipated. In a group of patients showing a higher average age, the accurate results will thus be decreased by the cases of endocervical carcinomas which may occur.

From 1953 through 1957, we have seen 13 cases of preclinical carcinoma in pregnancy (including three ectopic pregnancies) at the University Department of Obstetrics and Gynecology in Graz. Colposcopically we have obtained positive results in 12 cases. Correct cytological diagnosis (Papanicolaou Classes III, IV or V) were made in 11 cases. The women had an average age of 34.3 years. All the carcinomatous changes could be observed on the ectocervix.

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JULES-ANDRÉ BRET AND F. J. COUPEZ
Paris, France

Our own experience with this question is based upon three years of research which includes:

1. a systematic cytological smear from every patient,
2. a colposcopic examination of every patient with a suspicious smear or an abnormal cervix on speculum examination after the Schiller test.

3072 women have been examined; 4140 smears have been taken; 680 colposcopies performed and almost 250 biopsies done. The results are as follows:

Patients with cellular atypias according to class III, IV or V	33 = 1.1%
Patients with early invasive cancer	1 = 0.03%
Patients with cancer with doubtful invasion	1 = 0.03%
Patients with carcinoma in situ	12 = 0.4%
Patients with dysplasias of the type "unruhiges Epithel"	19 = 0.6%
Dysplasias of the type "abnormes Epithel"	14 = 0.5%

After evaluation of the results obtained during this experiment, certain statements may be made:

1. For lesions of the microcarcinomatous type and the carcinoma in situ there was no single case of discordance between colposcopical, histological and cytological examinations. When regressions were observed at the sites of the so-called "carcinomas in situ," they were confirmed later by these three methods after a certain period of time. First, colposcopy shows normalization of the surface. Then histology shows a decrease in severity, and finally, cytological findings begin to be normal.

2. The over-all results of the different methods also agree concerning the irregular dysplasias ("unruhiges Epithel" of the Zürich School), which may either regress or progress during or after pregnancy.

3. Where the regular dysplasias are concerned ("abnormes Epithel" Hinselmann I and II), the cytological reading always was class II, but they have only been tracked down by colposcopy.

4. Several smears with cellular atypias, and even two with a temporary Papanicoulaou class IV reading, did not show any suspicious lesion colposcopically or any dysplasia histologically. Cytological regression took place during the next few months.

The main source of error in pregnancy is the interpretation of the cellular changes caused by inflammation. Here, colposcopy reveals nothing other than inflammation. This must be pointed out for the clinicians who are sometimes rather disturbed by the diverging classifications of the different cytologists. For certain cytologists the presence of benign dysplastic cells justifies nothing more than class II, although they encounter a colposcopically extensive lesion.

Conclusion

We believe that the pregnancy in which the exfoliation rate is increased, is a favorable time for the cytological detection of cervical lesions, cancerous or precancerous, because the risks of false negative readings are diminished. However, the collaboration with colposcopy is indispensible for detection. It permits the guided biopsy of lesions which have become visible. It discovers, moreover, benign atypias which do not appear cytologically but may degenerate if not properly treated.

For research on and prevention of cervical lesions it seems to us the ideal solution would be the association of cytological with colposcopical examinations in the third and eighth month of every pregnancy and four months after delivery.

Until now we have only once seen negative smears where the corresponding histology revealed a carcinoma in situ, and where the lesion could also be seen in the colposcope.

Our conclusion after having discussed the quite different kinds of information yielded by the two methods is: "Don't oppose them--let them go together."

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DISCUSSION

ALFONSO ALVAREZ-BRAVO, Mexico, D.F., Mexico:

It is evident from the reports under consideration that the ideal procedure for detection of preclinical cancer of the cervix uteri should include both the cytological and the colposcopical examinations.

Our experience based upon ten years of the combined use of both methods (routine vaginal cytology in every patient and colposcopic examination of every patient with a suspicious smear or an abnormal cervix on speculum examination) fully agrees with the above opinion.

If we have to compare both methods, we must accept that cytology has a higher value for detection of cervical cancer and the reason has been clearly explained in Bajardi's paper concerning the carcinomatous changes of the endocervix.

We have had 11 cases of preclinical cervical carcinoma at the Gynecological Service of the Spanish Hospital of Mexico City, ten with positive cytology (Class IV or V) and seven with positive colposcopic findings, six of which were ectocervical cancers.

Moreover, the positive cytological findings are of higher value for detection as they show the presence of suspicious or definitely malignant cells whereas colposcopy will as a rule show only an abnormal epithelium.

However, the colposcopic examination is highly valuable because the cytological and the colposcopical findings do not agree in all cases. Actually, we have a clear-cut example in our series, in which the cytology was negative for cancer (Class II) and the diagnosis was suspected by colposcopy. Besides that, colposcopy is very useful in the management of suspicious cytological cases. It permits the guided biopsy of lesions not clearly visible macroscopically, which may lead to the histological confirmation of the diagnosis.

Therefore, it seems to us that the association of vaginal cytology and colposcopy is of real value in the detection of cervical cancer, provided that they are used routinely. The wise sentence of Bret and Coupez summarizes the question: "Don't oppose them - let them go together."

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CLARICE do AMARAL FERREIRA, Rio de Janeiro, Brazil:

As a matter of fact, for the detection of cancer in pregnant and non-pregnant women the usage of both methods, cytology and colposcopy, leads to increased accuracy.

By the experience of the Institute of Gynecology in Rio de Janiero, after examination of 10,000 patients, we have observed that cytology and colposcopy show approximately the same percentage of errors. However, commonly the errors do not occur on the same case, and thus we have the chance of repeating the examination when discrepancies exist, in order to see which technique failed. The point of view that the two methods ought to be employed together, has been defended and practiced by Professor Arnaldo de Moraes and his medical group here for ten years.

The accuracy of any method depends upon the interpreters. We have as colposcopist-in-chief an old pupil and assistant of Prof. Hinselmann, Dr. J. P. Rieper. I asked him about his opinion on the accuracy of colposcopy during pregnancy; he said: "During pregnancy, in 191 cases I have found recent cervical ectopics in 94 cases, with the corresponding dislocation of the squamo-columnar junction, which permits ideal colposcopic observation. This squamo-columnar junction is seen during colposcopic observation on the great majority of pre-invasive carcinoma cases. They develop after menopause, when the junction is visible, as Hamperl, et. al., have shown. Another fact, also known by the colposcopist, is that he can observe quite well the lower third of the cervical canal in the multiparous woman, who represents the majority of the candidates likely to have cervical carcinoma."

Dr. Rieper belives that the colposcopical diagnosis of carcinoma in situ is easier in the pregnant woman than in the non-pregnant woman. This is due to the fact that the lower part of the endocervix may be visualized during pregnancy. This contributes to the fact that colposcopy may be of great help in localizing the lesion during pregnancy for a bioptical diagnosis.

My point of view, as a cytologist not practicing colposcopy but working in a "team" with colposcopists and pathologists, is that both methods can show the same accuracy in the detection of preclinical cancer, especially if they are used by experts in the field.

JACQUES W. JENNY and HANS-ISELIN WYSS, Zürich, Switzerland:

We agree with Bajardi that colposcopy and cytology on ectocervical lesions apparently must have the same results, whereas in endocervical lesions which are not of great practical significance, the cytology should be more accurate. We refer to our discussion in this issue regarding colposcopy during pregnancy.

In our own series of examinations of nearly 500 pregnant women with combined colposcopy, cytology and histology, we found the following results:

	Discovered by		
	colp./cyt./hist.	Routine Cytology	Colposcopy alone
Carcinoma in situ	4 (0.8%)	2 (0.4%)	3 (0.6%)
Cases of atypical epithelium (not classified) (no controls or controls negative)	2 (0.4%)	2 (0.4%)	2 (0.4%)
Dysplastic ("unruhiges") epithelium	6 (1.2%)	2 (0.4%)	3 (0.6%)

It is known that colposcopy, as well as cytology, can give false negative results. The simultaneous use of both methods increases the accuracy, but this is economically not feasible. In our examinations we have found a higher percentage of marked histological changes than Bret and Coupez, since in all of our cases we combined colposcopy, cytology and histology. Applying either colposcopy or cytology alone, we would have arrived at the figures noted in the table, which are comparable to those of Bret and Coupez.

	Colposcopy		Cytology			
	pos.	neg.	Routine ex.		2nd examination	
			pos.	neg.	pos.	neg.
Carcinoma in Situ	3	1	2	2	4	0
Cases of Atypical epithelium (not classified)	2	0	2	0	2	0
Dysplastic ("unruhiges") Epithelium	3	3	2	4	6	0
Basal cell hyperactivity BCH I (& II)	2 (1 case missing)	2	1	4	1	4
Negative histolcgy	6	8	6	8	13	1
Total	16	14	13	18	26	5

Positive colposcopy: 146

Negative colposcopy: 339

If we compare the results of colposcopy and cytology, we find that colposcopy has about the same accuracy as routine cytological screening. Only on a second examination of the smears, performed by a single individual, with a special consideration of the question, is an accuracy of nearly 100% obtained. However, it is also obvious that colposcopy has more positive findings (146 cases) than cytology (13 cases on the first, 26 cases on the second examination). Therefore, the number of false positive results is much higher in colposcopy than in cytology.

It is our opinion that colposcopy and cytology should not compete with each other, but rather should supplement each other.

WARREN R. LANG, Philadelphia, Pennsylvania, U. S. A.:

Whether cytology or colposcopy is the preferred method of detecting cervical carcinoma in the pregnant woman depends, of course, upon many factors. Included among them are the previous training of the clinician, the availability of the method and the availability of competent judgment on the findings. Any screening technique must overlook carcinoma at some time or other.

Since squamous cell cervical carcinoma usually begins on the portio in the childbearing age, as Bajardi states, one would suppose that the two methods would be about equal in efficiency. This seems to correspond to the literature. In our experience colposcopy detects minor atypias which are often missed by the cytological smear. We would agree with Bret and Coupez that colposcopy affords a "guided" biopsy and that whenever possible a combination of both cytology and colposcopy is desirable.

HANS MUTH, Muenster i. Westfalen, Germany:

We agree with Bajardi, Bret and Coupez in that we could not prove the superiority of colposcopy over cytology in detecting carcinoma of the cervix uteri during pregnancy. In addition, however, the "Index of Malignancy" was markedly increased by cytodiagnosis. The colposcopical "Index of Malignancy" is the percentage of colposcopically discovered carcinomas in relation to the colposcopical atypical findings; the cytological "Index of Malignancy" is the percentage of cytologically discovered carcinomas as compared to the total of cytological atypical findings. In a total of 245 serial examinations we found colposcopically an atypical epithelium in 22 cases (= 9%) as compared to 5 positive results (=2.3%) with the cytological examination in the same series. Among these latter cases one was diagnosed colposcopically, as well as cytologically, as sub-clinical microcarcinoma. Thus the "Index of Malignancy" of colposcopy is 5%, the one of cytodiagnosis 20%.

In a histological screening project recently performed on 145 pregnant women, we detected in about 10% of all cases more or less accentuated epithelial atypias but only one carcinoma in situ. Interestingly enough only in one third out of the histologically proven epithelial atypias we also found cytological or colposcopical changes. Apparently there is no increase of cytological or colposcopical changes during pregnancy, whereas the histologically demonstrable epithelial atypias are markedly increased.

CLOSING REMARKS

FRIEDRICH BAJARDI:

According to my own experience I agree with the discussants when:

(A) they say that cytology results in a higher index of malignancy than colposcopy (Alvarez-Bravo, Jenny and Wyss, Muth),

(B) they emphasize the possibility of guided biopsies with the help of the colposcope (Alvarez-Bravo, Lang),

(C) they stress the advantages of the combined application of both techniques, cytology and colposcopy (Alvarez-Bravo, Lang).

The findings of Muth are very interesting and startling when he reports that he could find comparable atypical cytological or colposcopical patterns in merely one third of the histologically proven atypias during pregnancy. This is especially astonishing since by and large the cytological as well as colposcopical findings are based on the histological pattern of the cervical epithelium and, therefore, should reflect the comparable epithelial alterations. It would be important to receive more detailed information on this matter.

JULES-ANDRÉ BRET and F. J. COUPEZ:

In answer to the discussions on the results of colposcopy as compared to vaginal cytology during pregnancy, we can only express our deep satisfaction that the majority of the authors acknowledge the high diagnostic value of the joint application of both methods.

According to the opinion of the majority of the authors there are various cases which reveal false negative results. It seems that the supplemental application of both methods by trained people would be the only means by which the number of false negative results could be reduced to a minimum.

The advantage of the two-way search seems evident to us, for it allows colposcopically the detection of benign dysplasias not appreciated by cytology; we do not know about the future behavior of these dysplasias, particularly during subsequent pregnancies. It certainly would be reasonable to eradicate them as early as possible. On the other hand, colposcopy allows the irregular dysplasias to be followed very safely due to the possibility of guided biopsies which avoid a conization.

Without cytology and with only colposcopy, the number of biopsies is apt to increase needlessly and moreover endocervical lesions may easily escape detection.

In order to minimize the number of personnel involved we believe that the following scheme should be generally adopted:

1. Vaginal smear taken from every pregnant woman.
2. Colposcopy performed on every cervix which looks abnormal on speculum examination after application of the Schiller test.
3. Colposcopy and guided micro-biopsies done on every patient on whom the vaginal smear is Class 3, 4 or 5.

Thus, we hope that the detection procedure does not become too complicated and at the same time is given maximum efficiency.

SHOULD ALL PREGNANT WOMEN BE SCREENED FOR CERVICAL CARCINOMA?

EMMERICH von HAAM
Columbus, Ohio, U.S.A.

The average incidence of carcinoma of the cervix associated with pregnancy is 0.05%, or one case for every 2,000 obstetrical patients. Holzaepfel and Ezell (1) have reported that of 925 patients with carcinoma of the cervix observed in Columbus, Ohio between 1940 and 1957, 28, or 3% occurred in patients with an associated pregnancy. From these data the authors concluded that the combination of the two conditions is not rare and that "anyone entrusted with the care of female patients should maintain a high degree of suspicion." The incidence of intra-epithelial carcinoma during pregnancy is twice as high (approximately, 0.1%), according to Epperson and coworkers (2), while 20% of pregnant women show some degree of cervical basal cell hyperplasia with dyskaryosis (3).

Invasive cancer in the pregnant woman occurs in the younger age group and gives a poor prognosis when it is discovered during the last half of the third trimester (4). Intra-epithelial cancer will regress only in a small number of instances after termination of the pregnancy, according to Greene et al. (5), while dysplasia of pregnancy always disappears quite readily after its termination. Since intra-epithelial cancer is nearly always symptomless, it is easily overlooked on the usual prenatal examination. A routine Papanicolaou smear taken at the first prenatal and the first postnatal visit has been called the "epitome of clinical honesty" in pregnancy by McDuff (6). Montgomery (7) recommends a cytological examination of all patients at the onset of pregnancy, to be repeated at every instance of spotting or bleeding from the cervix and before treatment of any cervical erosion post partum.

In our obstetrical clinic, this plan is followed rigorously on all prenatal and postpartum patients. Smears are taken by the resident or the medical student after visualization of the cervix, using the wooden spatula. In the case of cellular dysplasia (Papanicolaou, Class II), we recommend that the smear be repeated at three to six month intervals until the normal cytological conditions have returned. When atypical cells are found suspicious for malignancy, we recommend that a smear be repeated within one month, to be followed by cervical biopsy. Our Department of Obstetrics feels that single, or even multiple, cervical biopsies may be done safely with proper precautions without interfering with a pregnancy.

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LEOPOLD G. KOSS
New York, New York, U.S.A.

While my experience with cervical cancer during pregnancy is a limited one, it seems quite logical that pregnancy, which brings a woman to her obstetrician and affords an average of one year of medical observation, represents an excellent opportunity to pick up cervical cancer. It is my experience,

and it has since been confirmed by others, that cervical cancer in pregnancy does not materially differ from cervical cancer in non-pregnant women. The complicating cytological factors such as trophoblastic cells, etc., will be of little disturbance to a trained eye and will not substantially alter the overall diagnostic accuracy.

I am certain that the question of treatment of cervical cancer in pregancy will be discussed by those more competent than myself. However, I cannot help emphasizing that carcinoma in situ is not a surgical emergency and that, in my experience, patients who are carefully watched can go through several pregnancies without a substantial alteration in the morphologic appearance of the lesion. The handling of invasive carcinoma will undoubtedly depend on the individual preference of the surgeon, and I do not feel competent enough to discuss it.

THOMAS A. SLATE

San Diego, California, U.S.A.

The time-honored method of speculum visualization of the cervix in every pregnant woman with biopsies of suspicious lesions has not been adequate in detecting carcinoma in situ and early incipient invasive carcinoma of the cervix. We all know that the most important single prognostic factor in carcinoma of the cervix lies in the earliest detection.

Routine cervical smears when combined with a speculum examination have proven to be the most practical and sensitive method of detecting carcinoma in situ and early incipient invasive carcinoma. This is especially important in pregnant women in whom minor or benign appearing cervical erosions or eversions become exaggerated and appear abnormal due to congestion and edema of the cervix as pregnancy progresses. In these conditions a negative smear would be of great assurance both to the physician as well as to the patient that an early carcinoma was not being missed.

Pregnancy will nearly always bring a patient to a physician's office or to a clinic for examination and prenatal care. Here lies a golden opportunity to screen patients, many of whom would not routinely lend themselves for examination and a Papanicolaou smear.

In our study of 10,044 pregnant women, there were five invasive carcinomas detected, three of these were unsuspected and would have been missed were it not for detection by the routine cervical smear. All three were early incipient lesions and received adequate treatment early in pregnancy, and thus were given the best opportunity for life. One of these patients was 20 years of age and had a Wertheim procedure with no positive nodes found.

The yield from routine screening of indigent pregnant patients definitely establishes the value of the cervical smear in detecting carcinoma of the cervix. This was particularly brought out in our study of indigent pregnant patients from the San Joaquin General Hospital. One cannot ignore detection of 6.5 to 8.6 carcinomas in situ per thousand pregnant women and two early invasive carcinomas from 1,385 pregnant women. The two early invasive carcinomas were not suspected and probably would not have been detected were it not for the routine smear. The ages of these two patients were 30 and 34 years.

In our studies the yield of early invasive carcinoma of the cervix and carcinoma in situ is necessarily less than in the non-pregnant, but when comparisons of the various age groups are made, the results nearly approximate one another. The incidence of carcinoma in situ in private, pregnant patients varies from 2.1 to 4.1 per thousand. This diagnosis of carcinoma in situ in pregancy is just as important, if not more so, than in the non-pregnant patient, even though some pathologists hesitate to make this diagnosis during pregnancy. We have shown that these lesions are real and in general persist throughout pregnancy and can be detected by routine smears. The detection of even one unsuspected, incipient invasive carcinoma of the cervix from 3,000 or even one from 6,000 pregnant women is very significant in that it may save this one life from an agonizing or prolonged death, notwithstanding the extreme expense of treatment, particularly if one is followed by ultra-radical surgery.

DISCUSSION

GEORGE J. ANDROS, Philadelphia, Pennsylvania, U.S.A.:

I am in whole-hearted agreement with the panelists in urging so-called "routine" cytological screening of all pregnant women. Since most asymptomatic women in the child-bearing age do not present themselves for pelvic examination, except during prenatal and early postnatal periods, pregnancy offers to the physician the best opportunity of detecting incipient and early cancer of the cervix at a time in the patient's life when many such lesions are apt to be found.

J. ERNEST AYRE, Miami, Florida, U.S.A.:

Pregnancy is one condition which always brings the patients to their physicians. Many of these might not otherwise seek medical examination. This provides a useful opportunity for cervical cytological

screening for carcinoma. It has been the writer's conviction that positive cancer cells found in cervical smears or scrapings signify the presence of carcinoma, whether the patient is pregnant or not. It has been our observation that minimal anaplastic or precancerous lesions will become accentuated during pregnancy. Many of these, including small areas of carcinoma in situ, will undergo involution but not regression, after the termination of pregnancy. It is, therefore, a favorable time for cytological screening to detect carcinoma in situ or early invasive lesions. It also provides an opportunity for applying preventive measures in patients showing precancerous or dyskaryotic tendencies or metaplastic or dysplastic lesions. Treatment need not be radical when the lesion is diagnosed as carcinoma in situ or as a lesser degree of neoplastic activity, but they must be kept under rigid control with frequent observation and rechecking by cervical cell scrapings. Carcinoma in situ found during pregnancy may be followed by monthly cell studies and then treated after the birth of the infant.

JULES-ANDRÉ BRET and FERNAND J. COUPEZ, Paris, France:

Our experience includes three years of systematic search for carcinoma during pregnancy, and we agree in considering cytology of great importance and practical value for mass screening.

Social point of view:

The circumstances of pregnancy are particularly favorable for cancer detection because they bring women to see their physicians thus offering a chance to follow them over a period of time. This is where the best chance lies in the search for carcinoma; there is much more difficulty in gynecological practice.

Medical point of view:

The hormonal as well as the anatomical conditions permit the detection of temporarily aggravated dysplastic lesions which, thus may more often be diagnosed by means of cytology. Although these lesions usually regress and although there are diagnostic difficulties in detection of carcinoma in situ lesions, these are not valid arguments against the search for carcinoma during this period.

Hence: The therapeutic decision is made only after some delay. The extent of therapy shall always be in agreement with the results of the last histological examination.

With our present ignorance concerning the probable development of benign, doubtful or suspicious lesions, we are very much interested in detecting and destroying these lesions as early as possible.

We realize that the number of dysplasias detected during pregnancy is infinitely larger than the number of invasive carcinomas diagnosed later. We are convinced, however, that future carcinomas stem from these dysplasias. Therefore, their destruction "a minima" (at this early stage of development) is actually the best prophylaxis enabling us to prevent cervical carcinoma at its early begining.

RONALD R. GREENE, Chicago, Illinois, U.S.A.:

There is an obvious concensus that all pregnant patients should be screened for carcinoma of the cervix. The subject need not be belabored further.

I suspect that the frequency of carcinoma of the cervix in pregnant patients is higher than the 0.05% quoted by von Haam and closer to the 0.21% to 0.41% in private patients and 0.65% to 0.86% in indigent patients given by Slate.

Dr. Koss's point that carcinoma in situ is not a surgical emergency is worth emphasizing. We have had experience with many patients with this diagnosis who have continued their pregnancy uneventfully. We would not recommend, however, that they be allowed to go through several pregnancies without definitive treatment.

JACQUES W. JENNY, Zürich, Switzerland:

All cases of carcinoma in situ and invasive carcinoma admitted to the University Hospital for Women, Zürich, from 1951-1957, were reviewed with the special consideration of how many had been detected incidentally during pregnancy or at the postnatal check-up three months post partum. Only those cases were selected which came to the hospital with symptoms other than those suspicious of carcinoma. All these women were less than 45 years old, most of them between 25-38. For this reason we compared our results not only with the total number of carcinomas, but also with the number of carcinomas found in women below the age of 45, since we found that this age gave a more correct answer to the above question.

Total number of cases 1951-1957	Carcinoma in situ	Stage I	Stage II	Stage III	Stage IV	Total Carcinoma
	125	130	209	156	33	653
Number of cases under 45 years of age	96	74	67	23	2	262
Cases discovered during prenatal check-up or prior to therapeutic abortion	8 6.4% 8.4%	5 3.8% 6.75%	1 0.48% 1.5%	0	0	14 2.65% 5.38%
Cases discovered during abortion	7 5.6% 7.3%	1 0.8% 1.35%	0	0	0	8 1.51% 3.08%
Cases discovered on check-up post partum (3 months post partum)	2 1.6% 2.1%	0	0	0	0	2 0.38% 0.38%
Total	17 13.6% 17.8%	6 4.6% 8.1%	1 0.48% 1.5%	0	0	4.54% 9.34%

Adding to this the number of cases with negative clinical findings, but with a suspicious smear or abnormal colposcopical findings during pregnancy or post partum, in whom eventually carcinoma was found, we arrive at the following figures:

Carcinoma in situ: 10 cases (8% resp. 10.4%)
Cervical Carcinoma Stage I: 5 cases (3.8% -- 6.7%)
Cervical Carcinoma Stage II: 0

On 500 unselected, pregnant women colposcopical and cytological examinations were performed during the second and third months of their pregnancy, combined with a biopsy of the anterior and posterior lip of the cervix. The results were as follows:

Type of lesion	Number of patients	Histology	Number of patients	Remarks
1. Invasive carcinoma	0		0	
2. Carcinoma in situ	4		4	(0.8%)
3. Cases of atypical epithelium (not classified)	1	Non-invasive atypical squamous epithelium	1	Patient did not return for further controls.
4. Suspicious cases	7	Non-invasive atypical squamous epithelium	1	Controls negative
		Dysplastic-atypical (unruhig-atypisches) epithelium	2	1 patient had controls negative 1 patient had controls positive
		Dysplastic-atypical	4	2 patients had controls negative 1 case: time of observation was too short for definite classification 1 case: no further control
5. Questionable suspicious cases	6	Basal cell hyperactivity (BCH I and II)	6	3 patients had controls negative 1 patient had control positive 2 cases: time of observation too short for definite classification

Attention is drawn to the following:

1. The overwhelming majority of apparently healthy women only have one gynecological examination during pregnancy.

2. The percentage of carcinomas, especially carcinoma in situ, detected incidentally during pregnancy or post partum is relatively high.

3. In a series of 500 pregnant women, four cases of true carcinoma in situ were found. One case of atypical epithelium could not be fully studied as the patient did not return for further examination. We believe that also the six suspicious and the six questionable (suspicious) cases are of a certain significance despite the possibility of spontaneous regression of these lesions.

4. The prognosis of cervical carcinoma is greatly influenced by early diagnosis and early treatment.

From the above we draw the conclusion that all women during pregnancy should be screened for carcinoma, and we agree with von Haam, Koss and Slate in this respect.

WARREN R. LANG, Philadelphia, Pennsylvania, U.S.A.:

Drs. von Haam, Koss and Slate, fully agree, as do I, that all pregnant women should be screened for carcinoma. Obstetric patients in our institution (1), as mentioned by von Haam, are examined with the speculum early in pregnancy and again just before delivery. Smears are taken routinely early in pregnancy and preceding postnatal cauterization. But, even if the smear is negative, biopsy is done if clinical findings alone suggest its necessity. Biopsies are taken frequently, the site usually being determined with the aid of the colposcope.

Although intra-epithelial cancer may be symptomless, this is by no means always the case (2).

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VIOLETTE M. NUOVO, Paris, France:

We completely agree with von Haam, Koss and Slate.

YOSEUP S. SONG, Providence, Rhode Island, U.S.A.:

The policies in regard to pregnant women in our screening project are exactly the same as those described by von Haam. We recommend that the vaginal aspiration smear be taken first, followed by a cervical scraping smear taken with a wooden spatula. The physicians describe the appearance of the cervix in each pregnant case. The incidence of invasive carcinoma of the cervix associated with pregnancy in our series is about 0.01%. Furthermore, we confirmed the fact that invasive cancer in pregnant women occurs in the younger age group. Based on the findings in our series, it is our belief that all pregnant women should be screened, and atypical smears should be repeated until normal cytological conditions recur.

CLOSING REMARKS

EMMERICH von HAAM:

It is gratifying that all discussants agree with the viewpoint of the speaker favoring screening of all pregnant women for carcinoma. The discrepancy in the incidence of carcinoma of the cervix in pregnant women is further emphasized by the figures of Song and Greene and probably means that no percentage figures are reliable with such a small number of cases. Jenny emphasizes the marked differences in the type of epithelial lesions discovered during or immediately after pregnancy. His figure of four cases of carcinoma in situ found in 500 pregnant women is certainly high.

EXFOLIATIVE CYTOLOGY AND COLPOSCOPY OF CERVICAL DECIDUAL REACTION

JULES-ANDRÉ BRET AND F. J. COUPEZ
Paris, France

Since Bayer's discovery (1885) of decidual cells in the cervix during pregnancy, many studies have been devoted to this question. The benignity of the lesion has hitherto concentrated the studies on only the clinical viewpoint of metrorrhagias graviditatis. Since the development of cytology and the problems connected with the influence of deciduosis on the cytological smear became acute, it seems to us that this occurrence deserves better knowledge. It is frequent and can, in certain cases (as shown in France by Lepage and Schramm) evoke a carcinoma.

Colposcopy, which we systematically apply on all our abnormal cervices, has taught us to recognize not all, but certain forms of the superficial deciduosis, the localization of which modifies in a certain manner the normal aspect of the organ.

From the size of sheets of decidual reaction and their localization in relation to the superficial layers of epithelium, we were able to observe:

1. A simple, initial form with discrete bulging and lifting up of the squamous epithelium in the vicinity of the external os. It is accompanied by a slightly darker color. Histologically the decidual sheet is separated, in this case on the surface by a strip of normal stroma.

2. A more pronounced form with a clear deformation of the external epithelial surface. We deal with an exophyte with large implantation base, of red or purple color which easily attracts attention. Histologically, the decidual group lies directly underneath the squamous epithelium. This can be intact with a positive Schiller test or, on the other hand, develop towards an ulceration with a negative Schiller test (Figs. 1, 2).

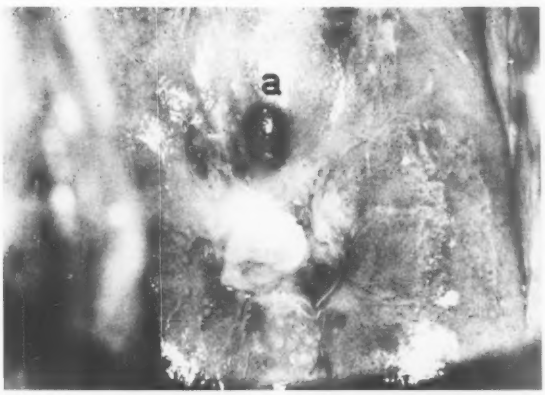

Fig. 1. Dedicual exophyte. The histology demonstrated a sheet surrounded by a decidual infiltration directly beneath the intact epithelium. Magnification 1.1x, acetic acid.

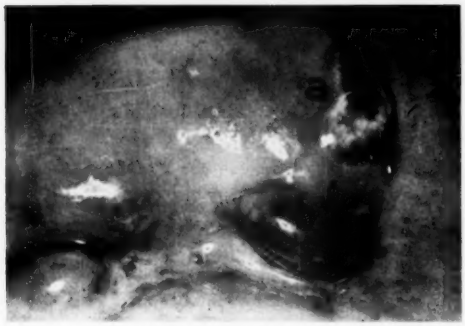

Fig. 2. Dedicual exophyte with intact epithelium (b) and ulcerated exophyte (a). These exophytes are iodine positive. Magnification 1.1x, acetic acid.

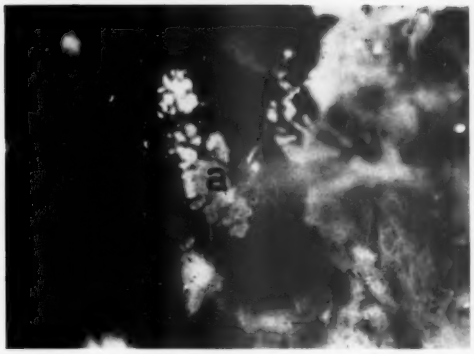

Fig. 3. Ulceration of a little sheet with the aspect of superficial deciduosis. The Schiller test shows that the ulceration is not complete. There is a little band of preserved epithelium persisting. Magnification 2x, Lugol.

3. Ulcerated forms:

The decidual hernia: This is a very small iodine negative exophyte with a narrow implantation base which acquires, under the action of acetic acid, a whitish surface, striped with a so-called leaf pattern. The histology at this site reveals the external hernia of a decidual sheet through a true collar of well-preserved epithelium (Fig. 3).

The decidual ulceration: This follows the disappearance of the squamous epithelium and may arise on the surface of an exophyte as well as at the site of extended sheet without superficial involvement. After application of acetic acid it presents itself as a striped white spot sometimes interrupted by intact epithelial stripes which are Schiller positive (Fig. 2a).

4. The ectropion of pregnancy and deciduosis:

The presence of decidual cells underlying a colposcopic cylindric ectopy is also sometimes apparent. This is generally a polypoid ectopy, very congested. The ulceration of glandular mucosa reminds one of the white and striped pictures which already have been described. The infection is always very pronounced in the sites of the ectopies of pregnancy and unfortunately, almost always prevents the formation of a characteristic form.

Conclusion:

The deciduosis can very often be found by systematic, histological examinations. Their clinical manifestations are very discrete. Superficial forms can colposcopically be recognized.

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ELIE TASSO, ANDRÉ RAUZY AND JEAN A. de BRUX
Paris, France

The diagnosis of cervical deciduosis is actually made from a few indicative signs in the cytological smear. It is especially its association with the pregnancy smear, coupled with certain rather exceptional cellular aspects, which leads one to suppose that the decidual transformation of the cervical stroma is under the influence of the hormones of pregnancy. In fact, the general aspect of the smear does not at first attract attention. The hormonal equilibrium does not appear disturbed: the levels of pyknosis and eosinophilia are very low or nil. Inflammation is frequent and, as in any pregnancy, is accompanied by a flora either varied or of Döderlein's bacilli, generators of a sometimes very accentuated cytolysis.

Nevertheless, certain cells of abnormal appearance are found, which constitute, in a measure, the test of a deciduosis. For only by a minute study of their morphology, at sufficient magnification, can one distinguish certain dyskaryotic squamous cells from true decidual cells as we shall define them.

CYTOLOGY OF THE IMPRINTS OF DECIDUA

For better acquaintance with the decidual cell, we have examined the imprints of 12 deciduae at term and from this study have defined the aspect of the decidual cell as compared with that of the other elements. Mixed in with blood and a few polynuclear cells, these three types of cells were distinguishable:

decidual cell
cytotrophoblast
syncytotrophoblast

The syncytotrophoblasts present no diagnostic problem: there are multinucleated cytoplasmic areas, or groups of naked nuclei; the nuclei are either side by side or piled up, rather small, round or oval, the strands of chromatin having small grains regularly distributed (Fig. 1).

The cytotrophoblasts are more difficult to distinguish from the decidual cells. These large elements, sometimes the size of an intermediate cell, have a cyanophilic or polychromatophilic cytoplasm of variable form: round, oval, or even quadrangular, with microvacuoles; the borders are sinuous, rather thick, folded, and under high magnification show small protuberances resembling pseudopods. The nucleus may be either central or somewhat peripheral, regular and round, with nucleolated chromatin composed of clearly visible grains. Sometimes there appear a few anomalies, marked by a slight festooning of the membrane or by a pale halo surrounding a nucleus of densified chromatin; at other points, the rather large nucleus is roughly folded in. These aspects seem to belong to "hypertrophied and globular" elements referred to by Dubreuil and Baudrimont in their treatise on histology and which, at the end of pregnancy, are the only vestiges of the trophoblastic elements of the basal lamina (Fig. 2).

On the smears of decidua, the decidual cell resembles large columnar cells, isolated or in loose clumps. Smaller than the cytotrophoblast, the size of an external basal cell, it has a grayish or pearl-toned cytoplasm, oval or elongated, of close texture, giving a microvacuolar, fine-grained appearance; the outlines are less distinct, and the double-ringed border less evident, than on the cervical biopsies. The nucleus, somewhat eccentric and situated at the extremity of the long vertical axis of the cell, is rather small and round, and the chromatin is very finely dotted. The dense texture of the cytoplasm and the fineness of the chromatin seem to us to represent the principal characteristics of the decidual cell as compared to the cytotrophoblast (Figs. 3, 3a, 3b).

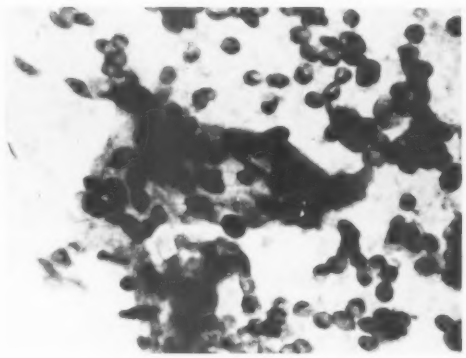

Fig. 1

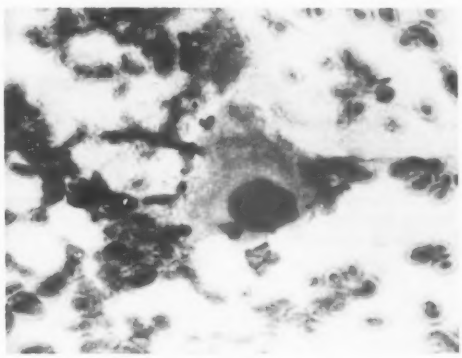

Fig. 2

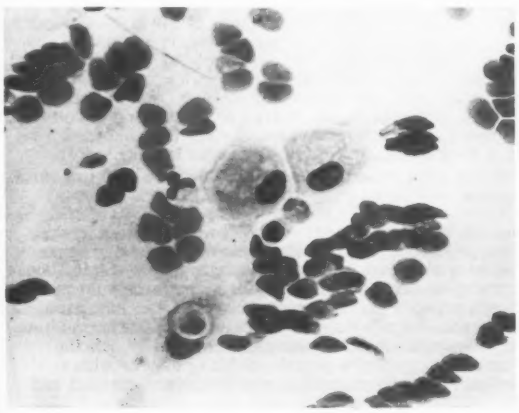

Fig. 3

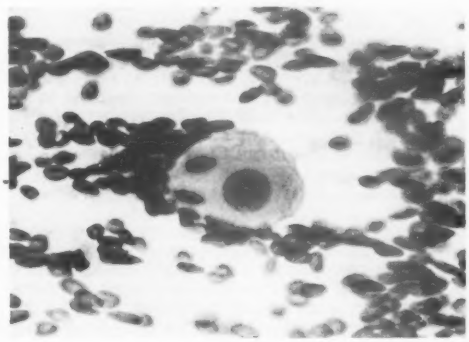

Fig. 3a

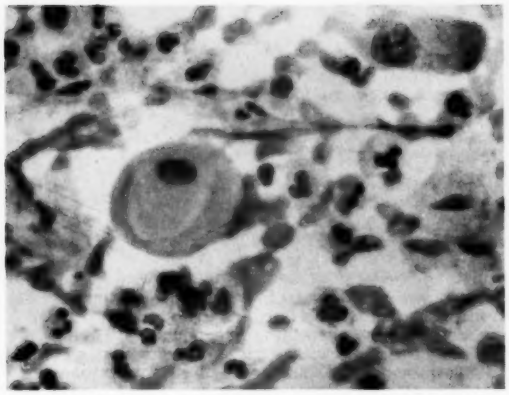

Fig. 3b

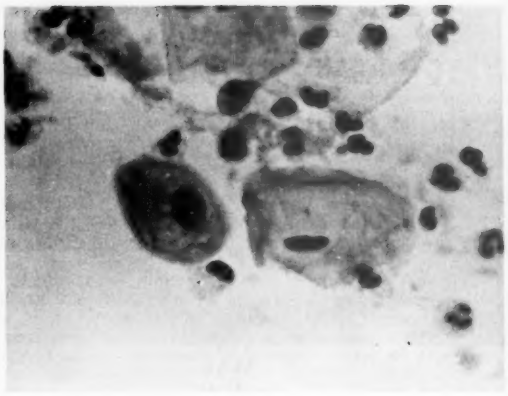

Fig. 4

DIFFERENTIAL MORPHOLOGICAL DIAGNOSIS

A close study of the decidual cell enables one rather rapidly to distinguish it from the other cellular elements:

(a) In the external basal cell, the nucleus, always centrally located, is larger in relation to the cytoplasm; the chromatin is less fine, more punctuated and more active than in the decidual cell; the cytoplasm is decidedly cyanophilic, dense, and without vacuoles, or if one exists it is usually only of moderate size; the cellular outlines are less distinctly traced, and above all, the double peripheral border is not found.

(b) In the navicular cell, of the same size or larger, one recognizes, a priori, the two most important distinctive characteristics of the decidual cell, the peripherally-located nucleus and the double outline; but the nucleus, while in fact eccentric, is no longer at the extremity of the long vertical axis but at that of the horizontal axis. It is, moreover, smaller, elongated, retracted and often irregular, with a transverse fold and a chromatin network barely visible.

Furthermore, the double outline of these cells results from the folding-in of the cellular edges, and hence the outer and the inner outlines are both very sinuous. The rest of the cytoplasm appears empty or with large vacuoles filled with glycogen, yellow- or even purple-tinged (Fig. 4).

ANOMALIES OF THE DECIDUAL CELLS AND THE CYTOLOGICAL DIAGNOSIS OF DECIDUOSIS

Deciduosis is difficult to diagnose, for, as emphasized, the individuality of the decidual cell is made up of fine degrees of differentiation. Furthermore, its desquamation is scanty and in the form of isolated cells. It should be remembered that this latter fact results from the erosion of the border, which is rather frequent, but involves only a very small zone. And the diagnosis becomes nearly impossible when the decidual cell presents anomalies, once the protective epithelium has disappeared; the differential characteristics are then no longer to be found. For instance, some decidual cells showing macro-vacuoles in their cytoplasm become almost identical to navicular cells, with the nuclei compressed and retracted (Fig. 5). The cells near the ulceration take a fibroid form, and sometimes their nuclei, having become dystrophic, bloated, pseudo-budding or shrunken, with more or less accentuated chromatin, likewise resemble fibroid squamous cells or a squamous cell with a dystrophic nucleus of the same type (Fig. 6). The difficulty increases from the fact that little cytoplasmic maturation takes place; nearly all of the cells remain cyanophilic. In some cases, moreover, the nucleus is almost pyknotic (Fig. 7).

Hence, it is understandable that many deciduoses pass unnoticed, or are considered as dyskaryoses, all the more easily because the decidual cells are difficult to recognize, whereas during pregnancy the border epithelium, squamous or columnar, takes on very abnormal cellular aspects under the influence of the potentialized or unbalanced hormonal factors. The epithelial anomalies, moreover, are very marked in the region of the zones of deciduosis, as if the connective tissue and the epithelium reacted in a parallel manner to the same stimuli. Thus, in many cases the deciduosis is evidenced in the form of intermediate or, more often, of parabasal type elements, with the nucleus either obese and very regular or, on the contrary, irregular, with chromatin folds and angular borders, giving a pseudo-budding aspect with two or three lobes. The chromatin usually remains pale and very regular, sometimes slightly distended and vacuolar (Fig. 8).

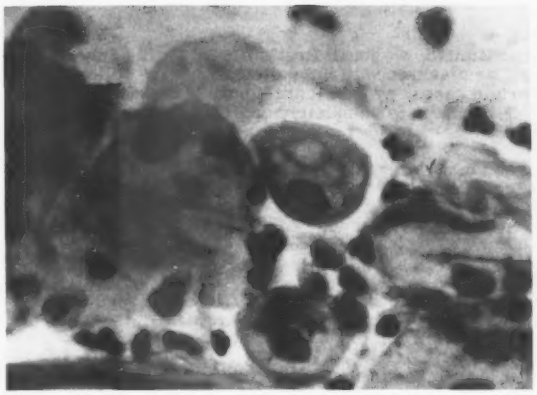

Fig. 5

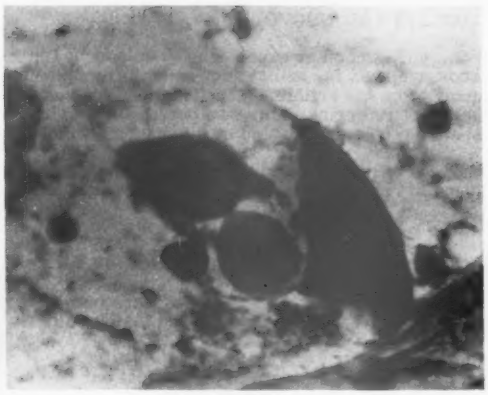

Fig. 6

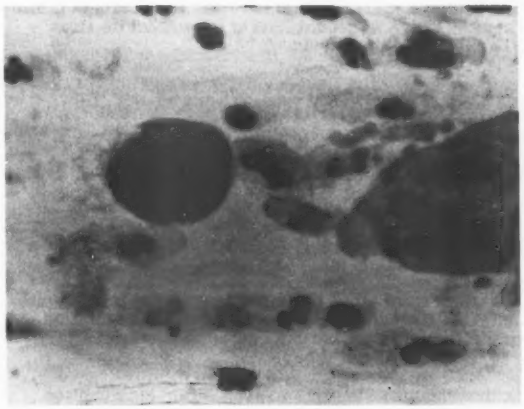

Fig. 7

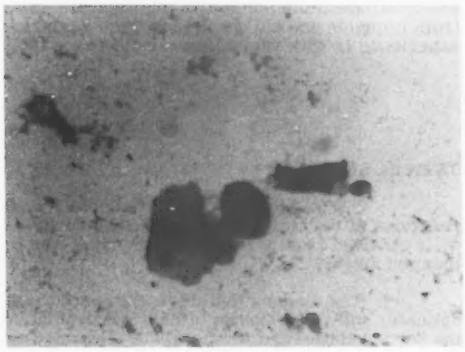

Fig. 8

All of these cellular peculiarities constitute the indirect signs of deciduosis, the cytological diagnosis of which cannot be made, a priori, on the decidual cells. This should, therefore, be borne in mind when one finds in a pregnant woman anomalies which are solely dyskaryotic in nature and not dysplastic. The rest of the examination should then be made under high magnification, in a search for true decidual cells, with their double outlines, microvacuolar cytoplasm, regular and eccentric nuclei, and their isolation in the midst of the other elements grouped in clumps.

Thus, the diagnosis of cervical deciduosis depends as much, if not more, on the covering elements as on the constitutive elements themselves. These facts reflect the extraordinary unity of the connective and epithelial tissues.

DISCUSSION

WARREN R. LANG, Philadelphia, Pennsylvania, U.S.A.:

Decidual reaction is a transformation of normal stroma into large polygonal cells with vesicular and relatively pale staining nuclei; a mosaic or tile-like pattern of cellular arrangement is observed. This process occurs in the endometrium and less noticeably in the cervix. Since the reaction may alter the surface by elevating the covering epithelium or may even be associated with ulceration, it is not surprising that decidual change may be suspected by both colposcopic and cytologic techniques. In our experience neither method is specifically diagnostic.

The authors' classification of colposcopic pictures of decidual reaction is an excellent one and would agree in the main with our findings.

VIOLETTE M. NUOVO, Paris, France:

Since our experience in colposcopy is rather limited, we found Bret's paper particularly instructive. As far as cytology is concerned, however, we disagree with his statements. The following quote from his article, "It is frequent and can, in certain cases, evoke a carcinoma," convinces us that he is not referring to his own personal experience. Our opinion is completely opposite, and our conviction seems to be corroborated by our experiences:

Routine cervical biopsies were taken from some 300 pregnant women. Only 13 of these were found to have evidence of decidual reaction. Cytological findings in these cases were:

(1) Negative. . . . . .9 cases
(2) Class III. . . . . .2 cases
(3) Class IV. . . . . .2 cases

The two Class IV cases were both confirmed by the follow-up. The two Class III cases had repeated biopsies. One case showed lesions closely resembling an intra-epithelial carcinoma; the other one only showed a polyp.

We wish again to stress that our two false cases of Class III were due to changes other than those caused by decidual reaction of the cervix.

Dr. de Brux's accurate description of decidual cells is indeed enlightening. But this interesting work seems to have been done only on decidual imprints. We would like to know if decidual cells can be easily differentiated on the vaginal smears, since there can be a marked difference between cells obtained from imprints and cells obtained from vaginal aspirations. Thus, we would like to know what de Brux's experience is with vaginal smears in cases of decidual reaction of the cervix.

CLOSING REMARKS

JEAN de BRUX:

If Violette Nuovo had extensively read our paper on the cytology and histology of the decidual reactions of the uterine cervix, she would have seen that the sole purpose of the description of the decidual cells obtained from a reading of imprints was to study these cells thoroughly and to be able to recognize them on smears.

The diagnostic differentiation of these cells from certain other cells on the smears is extremely delicate, and the presence of cervical deciduosis is indicated by indirect signs. In fact, the anomalies of the border epithelium (dyskaryosis of the squamous epithelium or atypia of the columnar epithelium) only lead us to suspect the existence of deciduosis.

Our cytological experience with cervical deciduoses consists of 12 cases. Without exception, the atypias encountered in these cases could not even be considered suspect. To evoke automatically a "suspicion of cancer," it is not sufficient to come upon a nuclear atypia; it must be studied and, if possible, analyzed. And this can be done with certainty only in the light of correlations with very precise histology, without which cytology is a relatively unfruitful process.

Our histological experience with cervical deciduoses has now reached 30 cases.

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NOTE: THE ABOVE LISTING INCLUDES THE PARTICIPANTS OF BOTH SYMPOSIA ON PREGNANCY CYTOLOGY (VOL. III, NOS. 1 & 2)

FUTURE SYMPOSIA

The following Symposia by Correspondence are being prepared at this time or are planned for the future issues of ACTA CYTOLOGICA:

SYMPOSIUM BY CORRESPONDENCE ON THE EFFECTS OF ENDOGENOUS ESTROGENS ON THE VAGINAL EPITHELIUM

SYMPOSIUM BY CORRESPONDENCE ON VARIOUS TECHNIQUES OF OBTAINING MATERIAL FOR CYTOLOGICAL STUDIES

SYMPOSIUM BY CORRESPONDENCE ON CARCINOMA IN SITU AND SO-CALLED PRECANCEROUS LESIONS

SYMPOSIUM BY CORRESPONDENCE ON ENDOCERVICAL ADENOCARCINOMA

SYMPOSIUM BY CORRESPONDENCE ON TRAINING OF CYTOTECHNOLOGISTS

SYMPOSIUM BY CORRESPONDENCE ON THE EFFECTS OF PREGESTATIONAL AGENTS (ENDOGENOUS AND EXOGENOUS PREGESTATIONAL SUBSTANCES)

SYMPOSIUM BY CORRESPONDENCE ON GASTROINTESTINAL CYTOLOGY

Individuals interested in participating in the above Symposia by Correspondence are invited to contact the Editorial Office for details. The three symposia listed on the top of this list are already closed; no new participants can be accepted. However, participants for the latter four symposia are welcome, and may be listed upon request.

There will be no more listing of details concerning the FUTURE SYMPOSIA in the journal because space does not permit listing all participants, topics, and the various deadlines for each individual symposium. This information is readily available by writing to the Editorial Office, 5841 South Maryland Avenue, Chicago 37, Illinois, U.S.A. Inquiries are invited.

SYMPOSIA UNDER CONSIDERATION

The following symposia have been suggested for consideration, but are not listed in the order of preference or chronology. The readers are invited to inform the Editorial Office in which of the symposia they would be most interested, so that an order of preference may be tentatively arranged.

1. Symposium on Tadpole-Shaped Squamoid Cells.
2. Symposium on Organization of Laboratory of Exfoliative Cytology.
3. Symposium on Cytological Studies in Amenorrhea.
4. Symposium on Cytology of Ascitic Fluid.
5. Symposium on Cytology of Malignant Tumors of Ovary and Tubes.
6. Symposium on Extra-Genital Cytology of Metastatic Gynecological Lesions.
7. Symposium on Phasemicroscopy and Other Special Microscopic Techniques.
8. Symposium on Training of Exfoliative Cytologists.
9. Symposium on Cytological Changes due to Microbiological Factors.
10. Symposium on the Comparative Diagnostic Accuracy, Efficiency and Specificity of Techniques for Detection of Carcinoma.
11. Symposium on Histiocytes.
12. Symposium on Cytological Microphotography.
13. Symposium on Cytological Terminology for Hormonal Evaluation.
14. Symposium on Quantitative Cytochemistry of Exfoliated Cells.
15. Symposium on Sex Chromatin.
16. Symposium on Vaginal Cytology During Childhood.
17. Symposium on Lung Cytology.
18. Symposium on Cytology of Exudates.
19. Symposium on Gastrointestinal Cytology.
20. Symposium on Endocervical Adenocarcinoma.
21. Symposium on Training of Cytotechnicians.
22. Symposium on Effect of Progestational Agents on the Vaginal Epithelium.

23. Symposium on Oral Cytology.
24. Symposium on Cytology of Nipple Discharge.
25. Symposium on Squamous Cell Carcinoma of the Cervix with Particular Emphasis on Micro-invasive Lesions.
26. Symposium on Incidence Statistics of Cervical Carcinoma.
27. Symposium on Tumor Cells in the Peripheral Blood.
28. Symposium on Terminology such as "Abnormal," "Suspicious," "Doubtful" and Others.
29. Symposium on the Menopause.
30. Symposium on the Normal Cervix (Cytology, Colposcopy, Colpomicroscopy, Histology).
31. Symposium on Cytology of the Large Intestine.
32. Symposium on Fluorescence Microscopy.
33. Symposium on the Significance and Interpretation of the Perinuclear Halo.
34. Symposium on Cytology of Adenocarcinoma of the Corpus.
35. Symposium on Metrorrhagia.

FORMS FOR CLINICAL INFORMATION AND LABORATORY REPORTS

Each laboratory of exfoliative cytology has its particular forms for obtaining clinical information and for issuing laboratory findings. The content of the form usually reflects the individual cytologist's particular field of interest in the field of exfoliative cytology.

Visitors to laboratories are usually interested specifically in these individual variations and in the forms used to convey information from the clinician to the cytologist and back to the clinician.

In this section ACTA CYTOLOGICA has selected a variety of forms for presentation. The forms are not reprinted for the purpose of obtaining uniformity. However, it might well be that some of the forms will give to the reader a perspective which might serve to improve his own forms.

The following forms reflect the specific interests of the cytologist, in addition to the local needs of his particular community. They are reprinted without comments except where the cytologist felt some explanation would be helpful for the understanding of the form.

The Editors

LAB. No.....

	NO CANCER CELLS FOUND
	ATYPICAL CELLS — But without abnormal features / With abnormal features
	CELLS SUSPECTED OF BEING MALIGNANT
	CONCLUSIVE MORPHOLOGY OF MALIGNANCY.

ADVISE:

	REPEAT IN.....
	BIOPSY; of Junctional Epithelium; of Endocervix.
	CURETTAGE

NOTES

.....SLIDES SATISFACTORY

.....SLIDES UNSATISFACTORY

LAB. No.....

UNIVERSITY OF EDINBURGH

DEPARTMENT OF OBSTETRICS & GYNAECOLOGY

CERVICAL AND VAGINAL SMEARS

PATIENT'S NAME ..... Date.....

Age..... Parity..... L.M.P.....

Cervical/Vaginal, Smear. OP/IP

COMPLAINT OR PRESENTING SYMPTOM.....

.....

CLINICAL DIAGNOSIS .....

RADIUM TREATMENT, with Date.....

HORMONE do. do. .....

CLINICAL OPINION OF CERVIX :
Intact Epithelium; Eroded; Benign; Suspicious; Malignant.

CLINICAL DISPOSAL : No treatment; W.L. indefinite; Given date for admission For Curettage; Biopsy cervix.

DOCTOR'S NAME .....

HOSPITAL..... WARD.....

.....
Signed

PREVIOUS BIOPSY AND SMEAR No.....

REPORT FROM: LAB NO._____

THE **CANCER INSTITUTE** AT MIAMI

Cancer Cytology Center

Division of Gynecytology

J. ERNEST AYRE, M.D. *Director*

1155 N. W. 14th STREET, MIAMI, FLORIDA

Telephone FR 1-5572

Date Reported _____ Date Received _____ Slide No. _____

GRADES OF CELL PATHOLOGY

GRADE 0	NORMAL cells — No cancer cells seen		
GRADE I	INFLAMMATORY Cell types — Probable Borderline or Reversibility	Hyperactive / Hyperplasia with precancerous tendencies	A / B
GRADE II	ANAPLASTIC cells of "PRECANCER CELL-COMPLEX" type	Indicative of a cytologic stage of cancer	MINIMAL May observe — A; MAXIMAL May consider surgery — B
GRADE III	Positive cells of FULLY-DEVELOPED CANCER type. __ Epidermoid Carcinoma __ mature __ undifferentiated Adenocarcinoma	Cells of preinvasive type / Suspicious cells of malignant morphology but inconclusive without biopsy / Conclusive evidence of malignancy	A / B / C

ATYPICAL CELLS (Questionable Nature)

Endogenous Estrogen (Cornification) for age or stage of sex cycle

__ Normal __ Hypo __ Hyper __ % cornification __ % pseudo-cornification

ADVISE

__ Recheck in 1 year

__ Recheck in ____ months

__ (Biopsy) (Curette) (Hysterectomy)

__ Multiple or serial sections through squamo-columnar junction (ring-biopsy) to confirm possible pre-clinical lesion.

__ Repeat "surface cell-biopsy" scraping from squamo columnar junction.

Remarks:

__ Slides satisfactory

__ Slides unsatisfactory

Interpreted by: _____

LAB NO. _____

THE **CANCER INSTITUTE** AT MIAMI

Cancer Cytology Center

J. ERNEST AYRE, M.D. *Director*

1155 N. W. 14th STREET, MIAMI, FLORIDA

Telephone FR 1-5572

GYNECYTOLOGY

Slide Date _____

Name of Patient _____ Race (19) _____ Age _____

From: Name _____

Address _____

PLEASE GIVE COMPLETE HISTORY FOR STATISTICAL TABULATION

Has patient had *previous cytology* in this laboratory? Yes ☐; No ☐; Lab. No. _____

Date LMP or menopause _____ Regular periods _____

Leucorrhoea _____ Length of cycle _____ days

Abnormal bleeding _____

Trichomonas Yes ☐; No ☐; Past history Trich. Yes ☐; No ☐

Now PREGNANT ____ mos.

No. full term ____ (25)

No. premature ____ (26)

No. abortions ____ (27)

No. living children ____ (28)

THERAPY

Hormones _____ Dose _____ Date _____

Vitamins _____

Radiation _____ Dose _____ Date _____

Nutritional appearance of patient:

Clinical appearance of CERVIX:

SURGERY:

FAMILY HISTORY CA:

TECHNIQUE USED

Surface cell biopsy _____

Cervical smear _____

Vaginal smear _____

Other _____

REMARKS:

Signature _____

JEAN BERGER, BASEL, SWITZERLAND

DEPARTMENT OF OBSTETRICS
AND GYNECOLOGY
UNIVERSITY OF BASEL
CYTOLOGY LABORATORY

UNIVERSITÄTS-FRAUENKLINIK
BASEL
Zytologisches Labor

NAME _____
DATE _____
SMEAR NO. _____

CANCER DIAGNOSIS
Name _____
Datum _____
Auftraggeber _____
Abstrichnummer _____

Ca-Zytodiagnostik

				V	P	C	E
Superficial cells			Oberflächl. Z.				
Intermediate cells			Intermediär Z.				
Basal cells			Basalzellen				
Cell Border:	marked	Zellgrenzen:	scharf				
	indistinct		unscharf				
	rolled		eingerollt				
Cell Size:	large	Zellgrösse:	gross				
	small		klein				
	intermediate		mittel				
Nucleus:	size	Kern:	Grösse				
	form: regular		Form: regelm.				
	irregular		unregelm.				
	chromatin content		Chromatingeh.				
Mitoses:	normal	Mitosen:	normal				
	abnormal		anormal				
	multinucleated		Mehrkernige Z.				
	spindle cells		Spindelzellen				
	tadpole cells		Schwanzzellen				
	histiocytes		Histiozyten				
	plasmocytes		Plasmozyten				
	endocervical cells		Endocervicale Z.				
	endometrial cells		Endometriale Z.				
	leukocytes		Leucozyten				
	erythrocytes		Erythrozyten				
	special cells		Bes. Zellen				
Remarks:		Bemerkungen:					
Short Description:		Kurze Beschreibung:					

Karyopyknotic Index: Karyopyknotischer Index:

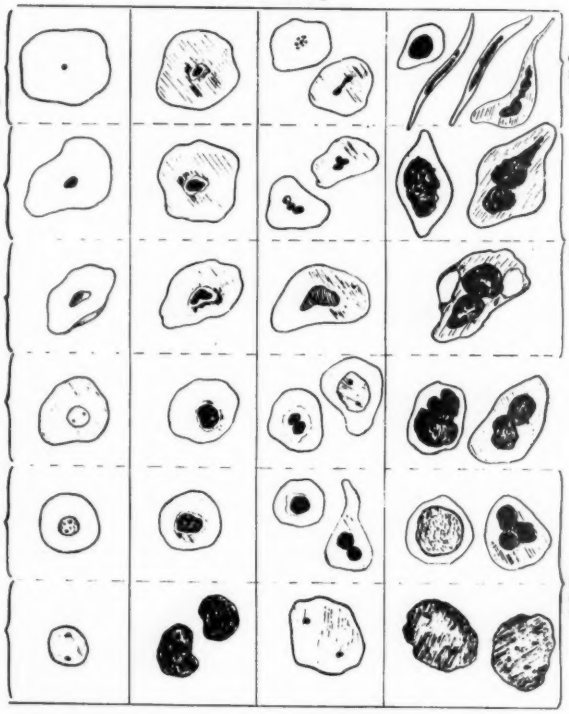
Acidophilic Index: Acidophiler Index:

Estrogenic effect: Oestrogen-Wirkung:

wenden!
See opposite side!

DIFFERENTIATION

Differenzierung



5 Keratinized squames	5 Horn-schuppen	differen-ziert reif	Mature
4 Superficial cells	4 super-ficial		
3 Inter-mediate	3 inter-mediär	poly-morph	Poly-morph
2 Parabasal	2 para-basal		
1 Basal	1 basal		
Free nuclei	Kern nackt	nicht differen-ziert	Undiffer-entiated

normal	entzündlich	anormal	atypisch
normal	inflammatory	abnormal	atypical

Bilder: _____ Kontrolle: _____

Diagnose: (negativ) KL I KL II (suspekt) KL III (positiv) KL IV KL V

Wiederholung: _____

Datum: _____ Untersucher: _____

Photographs: _____ Control: _____

Diagnosis: (negative) Class I Class II (suspicious) Class III (positive) Class IV Class V

Repeat smears: _____

Date: _____ Interpreter: _____

HANNS WERNER BOSCHANN, WEST-BERLIN, GERMANY

NAME: AGE: years ADDRESS:

Menstrual History: L. M. P. days ago

MENOPAUSE years ago

Previous Radium or X-ray Therapy:

Previous Sex Hormone Therapy:

1. for cancer screening
2. for differential diagnosis
3. for hormonal evaluation (ovarian function or administered hormones)

(UNDERLINE WHAT APPLIES)

TYPE of PREPARATION of SMEARS:

a) vaginal fornix:
b) cervical scraping:
c) endocervix:
d) intrauterine aspiration:

Report Requested by Phone

Tel. No.

If smear is repeated, previous No.

CLINICAL DIAGNOSIS:

QUESTION:

DOCTOR: (date & signature)

The smears must be fixed prior to air-drying. We recommend fixing the smears for at least 15 minutes in a mixture of 95% alcohol-ether (50:50) or a mixture of 95% alcohol - 85% glycerin (80:20). For hormonal evaluation, smears should be prepared from the lateral vaginal wall. For cancer detection we request a smear from the vaginal fornix, the uterine cervix and the endocervix. The smears from the fornix and the cervix are prepared with an ordinary spatula and from the endocervix with a small platinum loop which is introduced 10 to 20 mm into the endocervix and withdrawn with a rotating movement. When the presence of an intrauterine neoplasm is suspected an intrauterine aspiration is recommended with a dull cannula or with a fine polyethylene cannula attached to a glass syringe.

The smears should be prepared prior to digital examination and prior to any other intravaginal treatment or procedure.

CYTOLOGIC FINDINGS:

CANCER READING:

1. Not suspicious.
2. Atypical, but not suspicious
3. Suspicious, but not diagnostic
4. Highly suspicious
5. Smears compatible with atypical epithelial proliferation (ca in situ or invasive ca)

I. Repeat smear requested
II. Permanent control requested
III. Repeat smear 3-5 days after injection of 10 mg estradiol benzoate to obtain final evaluation
IV. No reading possible: dried before fixation / too many red blood cells

DEGREES OF DÖDERLEIN: I, II, III, IV

a) predominantly B. vag. Döderlein
b) predominantly cocci
c) Trichomonads, fungi

HORMONAL EVALUATION:

1. Findings are/are not compatible with menstrual history or age of patient
2. Marked estrogen effect
3. Normal folliculin hormone production
4. Slightly hypoestrogenic
5. Markedly hypoestrogenic with epithelial atrophy
6. Apparently androgenic effect
7. Apparently progestational effect
8. Cytologically may be pregnancy
9. No hormonal reading possible from present material

INFLAMMATORY REACTION:

1. No inflammatory reaction
2. Acute inflammatory reaction
3. Chronic inflammatory reaction

CONTROL No.

(Date & Signature)

PREPARATION OF SMEARS BY THE PHYSICIAN

(1) Vaginal Fornix

The smears are best done prior to digital gynecological examination. Three different sites are smeared for each examination. All three can be put on one glass slide but should be kept apart. If several patients are examined in a row it is advisable to mark the slides with a diamond pencil.

Figure 1
After insertion of the vaginal speculum some secretion is taken from the vaginal fornix without any scraping. The material is smeared thinly on a glass slide.

(2) Uterine Cervix

Figures 2 (a) and 2 (b)
Another smear is prepared without marked scraping from the squamous-columnar junction:
(a) if no ectropion or erosion present: from external os
(b) if ectropion or erosion present: at the border of the ectropion or erosion.

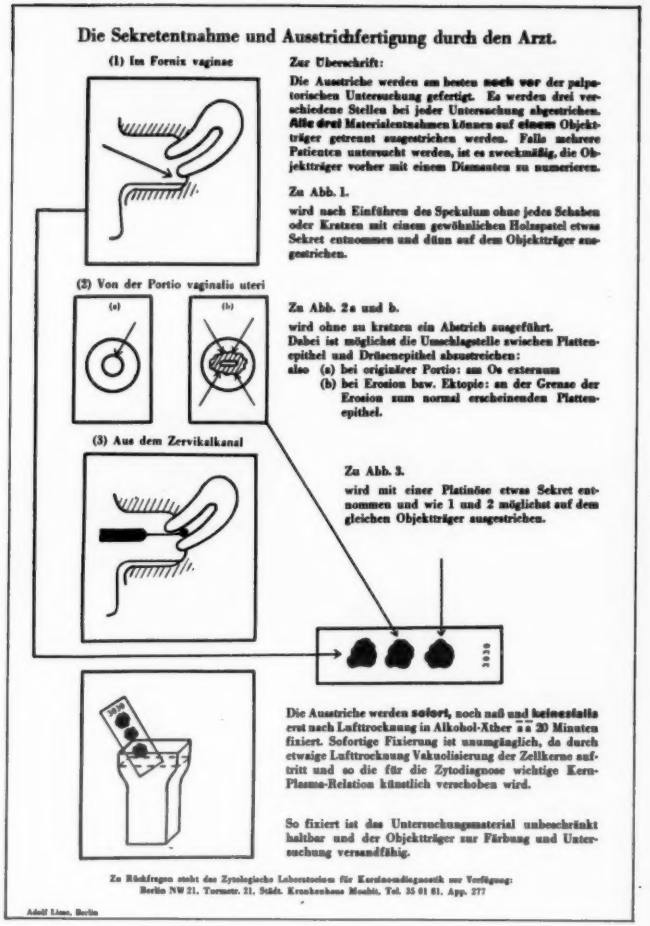
(3) Cervical Canal

Figure 3
Another smear will be taken with a small platinum loop and smeared on the same glass slide as (1) and (2).

The smears are immediately fixed while still wet and under no circumstances after air-drying. The fixation is done in alcohol-ether for approximately twenty minutes. The immediate fixation is important since nuclear vacuolization appears as a result of air drying which results in an artifical change of the diagnostically important nuclear-cytoplasmic ratio.

Fixed in this manner, the smears are permanently preserved and the glass slide is ready to be mailed for staining and examination.

For further information call the Cytology Laboratory for Cancer Detection: Moabit Hospital, 21 Turmstrasse Berlin NW21, Tel. No. 350181, extension 277.



JOSÉ BOTELLA LLUSIA AND LUIS MONTALVO RUIZ
MADRID, SPAIN

UNIVERSITY OF MADRID

MEDICAL FACULTY

II. GYNECOLOGICAL CLINIC — Prof. Botella Llusia

Department of Gynecological Cytology - Dr. Montalvo

Patient — No.
Age — Marital Status

Menstrual history: Normal, amenorrhea, oligomenorrhea, hypermenorrhea
Metrorrhagia, Menorrhagia. Pregnant: yes, no. Weeks of gestation _____
Post-partum _____.

Abortion: threatened, eminent, complete.

Hormonal therapy _____ when? _____ name of hormone _____

Radiation therapy _____ dosage? _____ dates? _____

Radiotherapy _____ dosage? _____ dates? _____

Clinical data: Negative, vaginitis, cervicitis, endocervicitis, erosion, suspicious lesion, contact bleeding, post-menopausal bleeding, _____

Colpocytological findings: Cellular atypia _____

_____

Hormonal cytology:

VAGINAL CYTOGRAM

Date of smear	basal cells	parabasal cells	intermediate cells	superficial cells	folding	acido-philic	wbc	class-ification

REMARKS _____

_____ Date _____

_____

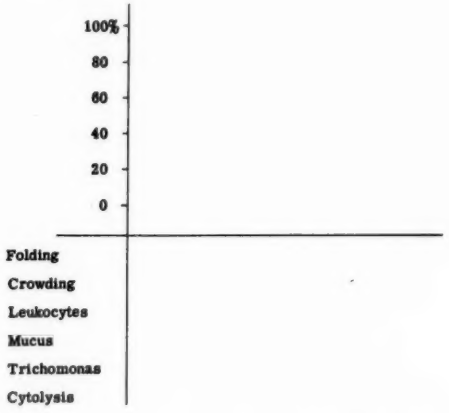
UNIVERSITY OF PARIS
GYNECOLOGICAL CLINIC - HOSPITAL BROCA
PROFESSOR P. FUNCK -BRENTANO

COLPOCYTOLOGY (Assoc. Prof. J. de Brux) No.:

NAME of the patient: AGE:

Examination requested by doctor: Date:

Date of last menstrual period:



CONCLUSIONS Examination done by:

GYNECOLOGICAL CLINIC - HOSPITAL BROCA
PROFESSOR P. FUNCK -BRENTANO

REQUEST FOR COLPOCYTOLOGY EXAMINATION

Room Bed Consultation Sterility Problem

Doctor Date

Name of patient: Age:

Address:

Clinical diagnosis: Normal cervix, inflammatory disease, dystrophy, neoplasm*

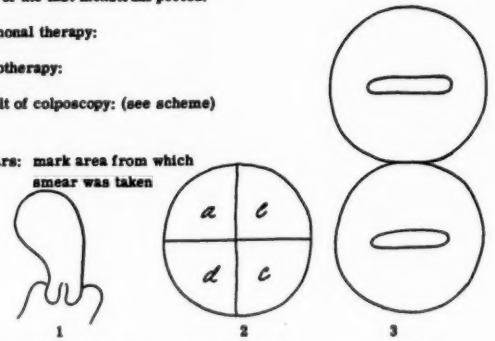
Date of the last menstrual period:

Hormonal therapy:

Radiotherapy:

Result of colposcopy: (see scheme)

Smears: mark area from which smear was taken



*Cross out diagnoses which do not apply.

PAUL FUNCK-BRENTANO AND JEAN DE BRUX,
PARIS, FRANCE

CLAUDE GOMPEL, BRUSSELS, BELGIUM

INSTITUT JULES BORDET

CENTRE DES TUMEURS DE L'UNIVERSITE LIBRE DE BRUXELLES

1, rue Héger-Bordet, Bruxelles

—

CYTOLOGIE GENITALE

NOM & PRENOM AGE

Date du prélèvement Consultation ☐ Etage ☐

Type du prélèvement : Frottis vaginal cervical endometrial

Date des dernières règles :

Rythme des dernières règles :

Médications hormonales reçues :

Autres renseignements cliniques :

Examens cytologiques antérieurs : N°

Prélevé par le Dr:

Protocole Cytologique

Date

Aspect du frottis : Flore microbienne :

Leucocytes : Hématies : Histiocytes :

CELLULES VAGINALES MALPIGHIENNES

CELLULES CERVICALES
1. exocervicales

2. endocervicales

CELLULES ENDOMETRIALES

AUTRES ELEMENTS CELLULAIRES

CONCLUSION

CYT.
10A

CYTOLOGY OF FEMALE REPRODUCTIVE TRACT

NAME & FIRST NAME _____ AGE _____

DATE _____ Consultation _____ Floor _____

Type of material: vaginal cervical endometrial

L. M. P. _____

History of last cycles: _____

Hormonal therapy: _____

Other clinical information: _____

_____

_____

Previous cytological examination: NO: _____

_____ Smears made by Dr: _____

CYTOLOGY REPORT

Date:

General appearance of smear: Microbiology:

Leukocytes: Erythrocytes: Histiocytes:

VAGINAL SQUAMOUS EPITHELIAL CELLS

CERVICAL CELLS

1. ectocervical
2. endocervical

ENDOMETRIAL CELLS

OTHER CELLULAR FEATURES

CONCLUSION

RUTH M. GRAHAM, BUFFALO, NEW YORK, U.S.A.

ROSWELL PARK MEMORIAL INSTITUTE

Buffalo 3, New York

CYTOLOGICAL EXAMINATION

HOSPITAL #_____

NAME: _____ **Age:** _____ **Date:** _____

Clinic: _____ **Ward:** _____

Source of Smear: _____

Has Patient had radiation therapy: **Yes** **No**

RESULTS: **Positive**

Negative

Doubtful

Unsatisfactory

REMARKS:

Form 808

THE OHIO STATE UNIVERSITY
UNIVERSITY HOSPITAL

REPORT OF PATHOLOGIST

C2617

Service *Date* 6-14-58 *Hosp. No.* 633078 *O.P. No.*

Name Mrs. Jane Doe *Age* 35 *Nursing Unit* 7C

Clinical Diagnosis R/O carcinoma, cervix.

Findings:

Cervical smear:

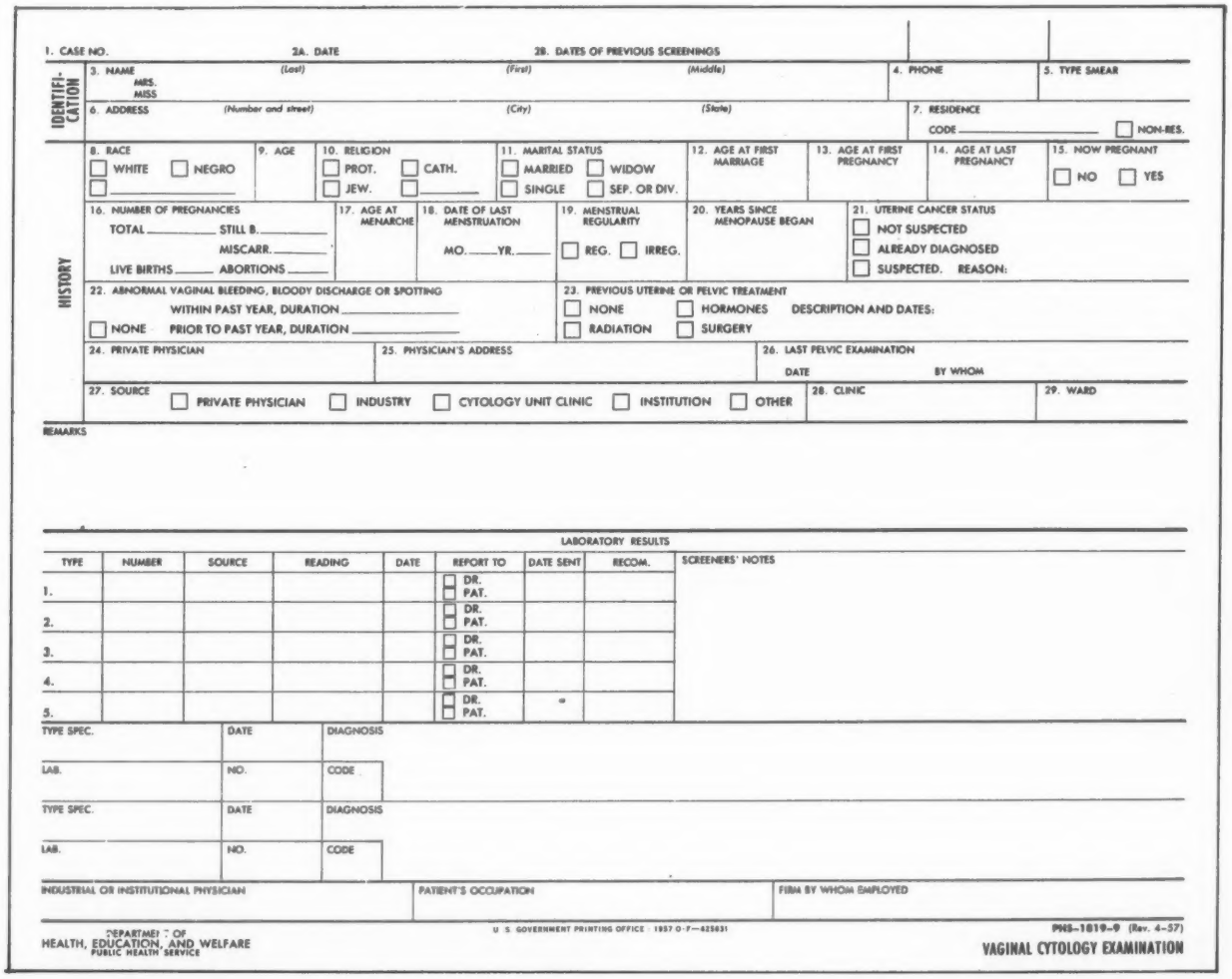
Estrus	2+
Infection	1+
Hemorrhage	Neg.
Pap Class	I - trichomonas.

Classification of malignancy.

Class I: Absence of atypical or abnormal cells
Class II: Atypical cytology but no evidence of malignancy
Class III: Cytology suggestive of, but not conclusive of malignancy
Class IV: Cytology strongly suggestive of malignancy
Class V: Cytology conclusive of malignancy

Signed
Guenther Ceelen, M.D. Pathologist

7



1. CASE NO. | 2A. DATE | 2B. DATES OF PREVIOUS SCREENINGS

IDENTIFICATION

3. NAME (Last) (First) (Middle) | 4. PHONE | 5. TYPE SMEAR

6. ADDRESS (Number and street) (City) (State) | 7. RESIDENCE CODE ____ ☐ NON-RES.

HISTORY

8. RACE ☐ WHITE ☐ NEGRO ☐ ____ | 9. AGE | 10. RELIGION ☐ PROT. ☐ CATH. ☐ JEW. ☐ ____ | 11. MARITAL STATUS ☐ MARRIED ☐ WIDOW ☐ SINGLE ☐ SEP. OR DIV. | 12. AGE AT FIRST MARRIAGE | 13. AGE AT FIRST PREGNANCY | 14. AGE AT LAST PREGNANCY | 15. NOW PREGNANT ☐ NO ☐ YES

16. NUMBER OF PREGNANCIES TOTAL ____ STILL B. ____ MISCARR. ____ LIVE BIRTHS ____ ABORTIONS ____ | 17. AGE AT MENARCHE | 18. DATE OF LAST MENSTRUATION MO. ____ YR. ____ | 19. MENSTRUAL REGULARITY ☐ REG. ☐ IRREG. | 20. YEARS SINCE MENOPAUSE BEGAN | 21. UTERINE CANCER STATUS ☐ NOT SUSPECTED ☐ ALREADY DIAGNOSED ☐ SUSPECTED. REASON:

22. ABNORMAL VAGINAL BLEEDING, BLOODY DISCHARGE OR SPOTTING WITHIN PAST YEAR, DURATION ____ ☐ NONE PRIOR TO PAST YEAR, DURATION ____ | 23. PREVIOUS UTERINE OR PELVIC TREATMENT ☐ NONE ☐ HORMONES ☐ RADIATION ☐ SURGERY DESCRIPTION AND DATES:

24. PRIVATE PHYSICIAN | 25. PHYSICIAN'S ADDRESS | 26. LAST PELVIC EXAMINATION DATE BY WHOM

27. SOURCE ☐ PRIVATE PHYSICIAN ☐ INDUSTRY ☐ CYTOLOGY UNIT CLINIC ☐ INSTITUTION ☐ OTHER | 28. CLINIC | 29. WARD

REMARKS

LABORATORY RESULTS

TYPE	NUMBER	SOURCE	READING	DATE	REPORT TO	DATE SENT	RECOM.	SCREENERS' NOTES
1.					☐ DR. ☐ PAT.			
2.					☐ DR. ☐ PAT.			
3.					☐ DR. ☐ PAT.			
4.					☐ DR. ☐ PAT.			
5.					☐ DR. ☐ PAT.			

TYPE SPEC.	DATE	DIAGNOSIS
LAB.	NO.	CODE
TYPE SPEC.	DATE	DIAGNOSIS
LAB.	NO.	CODE

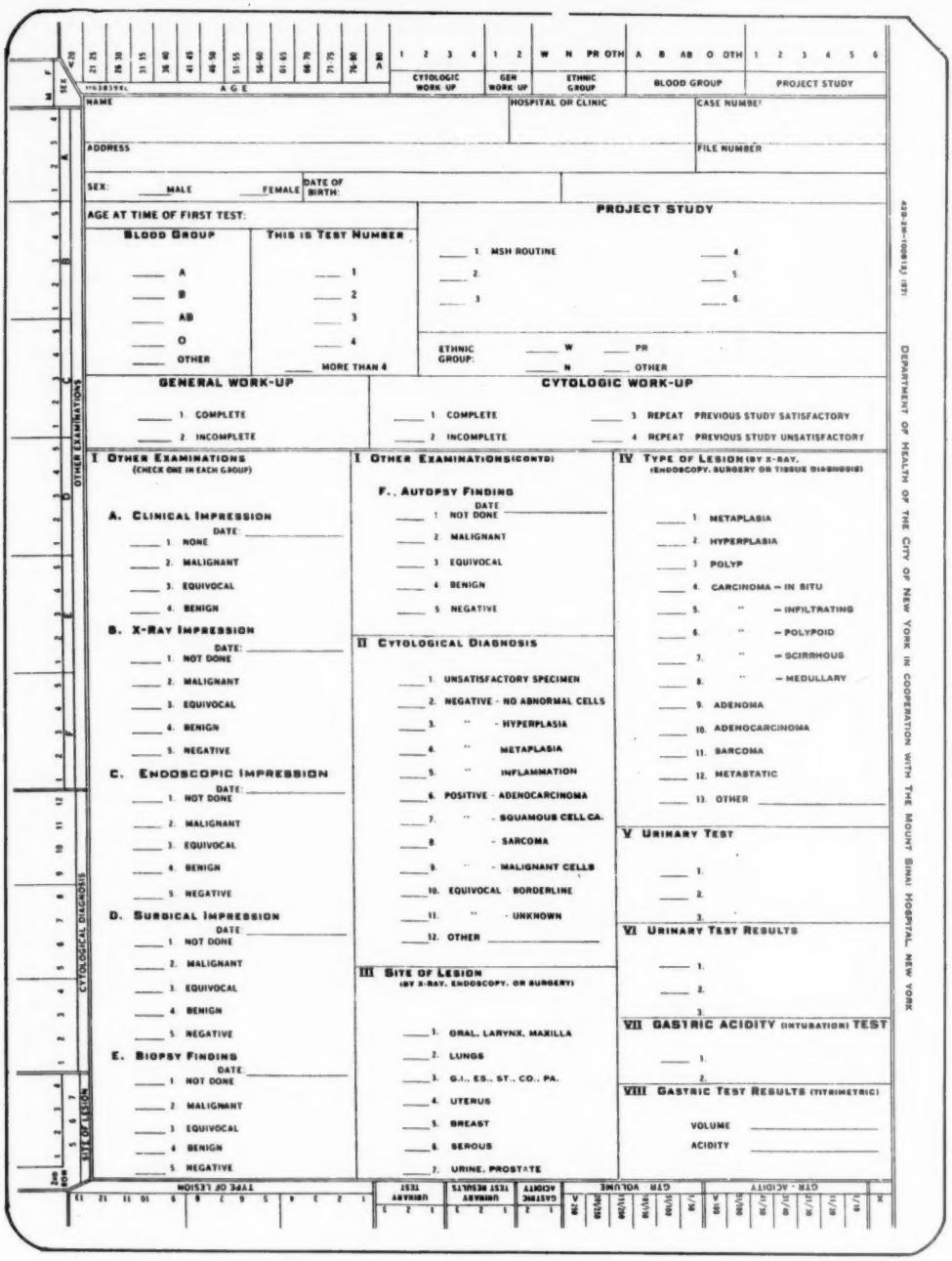
INDUSTRIAL OR INSTITUTIONAL PHYSICIAN | PATIENT'S OCCUPATION | FIRM BY WHOM EMPLOYED

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE

U. S. GOVERNMENT PRINTING OFFICE : 1957 O-F—425831

PHS–1819–9 (Rev. 4–57)

VAGINAL CYTOLOGY EXAMINATION



SEX: M F

AGE: <20 | 21-25 | 26-30 | 31-35 | 36-40 | 41-45 | 46-50 | 51-55 | 56-60 | 61-65 | 66-70 | 71-75 | 76-80 | >80

CYTOLOGIC WORK UP: 1 2 3 4

GEN WORK UP: 1 2

ETHNIC GROUP: W N PR OTH

BLOOD GROUP: A B AB O OTH

PROJECT STUDY: 1 2 3 4 5 6

NAME

HOSPITAL OR CLINIC

CASE NUMBER

ADDRESS

FILE NUMBER

SEX: ____ MALE ____ FEMALE

DATE OF BIRTH:

AGE AT TIME OF FIRST TEST:

BLOOD GROUP

____ A
____ B
____ AB
____ O
____ OTHER

THIS IS TEST NUMBER

____ 1
____ 2
____ 3
____ 4
____ MORE THAN 4

PROJECT STUDY

____ 1. MSH ROUTINE
____ 2.
____ 3
____ 4.
____ 5.
____ 6.

ETHNIC GROUP: ____ W ____ PR ____ N ____ OTHER

GENERAL WORK-UP

____ 1. COMPLETE
____ 2. INCOMPLETE

CYTOLOGIC WORK-UP

____ 1. COMPLETE
____ 2 INCOMPLETE
____ 3 REPEAT PREVIOUS STUDY SATISFACTORY
____ 4 REPEAT PREVIOUS STUDY UNSATISFACTORY

I OTHER EXAMINATIONS (CHECK ONE IN EACH GROUP)

A. CLINICAL IMPRESSION DATE: _____

____ 1. NONE
____ 2. MALIGNANT
____ 3. EQUIVOCAL
____ 4. BENIGN

B. X-RAY IMPRESSION DATE: _____

____ 1. NOT DONE
____ 2. MALIGNANT
____ 3. EQUIVOCAL
____ 4. BENIGN
____ 5. NEGATIVE

C. ENDOSCOPIC IMPRESSION DATE: _____

____ 1. NOT DONE
____ 2. MALIGNANT
____ 3. EQUIVOCAL
____ 4. BENIGN
____ 5. NEGATIVE

D. SURGICAL IMPRESSION DATE: _____

____ 1. NOT DONE
____ 2. MALIGNANT
____ 3. EQUIVOCAL
____ 4. BENIGN
____ 5. NEGATIVE

E. BIOPSY FINDING DATE: _____

____ 1 NOT DONE
____ 2 MALIGNANT
____ 3 EQUIVOCAL
____ 4 BENIGN
____ 5 NEGATIVE

I OTHER EXAMINATIONS (CONTD)

F., AUTOPSY FINDING DATE: _____

____ 1 NOT DONE
____ 2 MALIGNANT
____ 3 EQUIVOCAL
____ 4 BENIGN
____ 5 NEGATIVE

II CYTOLOGICAL DIAGNOSIS

____ 1. UNSATISFACTORY SPECIMEN
____ 2. NEGATIVE - NO ABNORMAL CELLS
____ 3. " - HYPERPLASIA
____ 4. " METAPLASIA
____ 5. " INFLAMMATION
____ 6. POSITIVE - ADENOCARCINOMA
____ 7. " - SQUAMOUS CELL CA.
____ 8. - SARCOMA
____ 9. " - MALIGNANT CELLS
____ 10. EQUIVOCAL - BORDERLINE
____ 11. " - UNKNOWN
____ 12. OTHER _____

III SITE OF LESION (BY X-RAY, ENDOSCOPY, OR SURGERY)

____ 1. ORAL, LARYNX, MAXILLA
____ 2. LUNGS
____ 3. G.I., ES., ST., CO., PA.
____ 4. UTERUS
____ 5. BREAST
____ 6. SEROUS
____ 7. URINE, PROSTATE

IV TYPE OF LESION (BY X-RAY, ENDOSCOPY, SURGERY OR TISSUE DIAGNOSIS)

____ 1 METAPLASIA
____ 2. HYPERPLASIA
____ 3 POLYP
____ 4. CARCINOMA — IN SITU
____ 5. " — INFILTRATING
____ 6. " — POLYPOID
____ 7. " — SCIRRHOUS
____ 8. " — MEDULLARY
____ 9. ADENOMA
____ 10. ADENOCARCINOMA
____ 11. SARCOMA
____ 12. METASTATIC
____ 13. OTHER _____

V URINARY TEST

____ 1.
____ 2.
3.

VI URINARY TEST RESULTS

____ 1.
____ 2.
3.

VII GASTRIC ACIDITY (INTUBATION) **TEST**

____ 1.
2.

VIII GASTRIC TEST RESULTS (TITRIMETRIC)

VOLUME _____
ACIDITY _____

OTHER EXAMINATIONS
CYTOLOGICAL DIAGNOSIS
SITE OF LESION
2nd Row
TYPE OF LESION: 11 12 13 14 15 16 17 18 19 20 21 22
URINARY TEST: 1 2 3
URINARY RESULTS: 1 2 3
GASTRIC ACIDITY: 1 2
GTM VOLUME: V 1-2M 1M/2M 1/2M 1/4M 1/8M
GTM - ACIDITY: 1/8 1/16 1/32 1/64 1/128 1/256 1/512 1/1024 1/2048 1/4096 1/8192 1/16384 1K

439-2M-10(61) 1971

DEPARTMENT OF HEALTH OF THE CITY OF NEW YORK IN COOPERATION WITH THE MOUNT SINAI HOSPITAL, NEW YORK

IX DATE CYTOLOGICAL SPECIMEN COLLECTED: _____

X CYTOLOGICAL TEST PROCEDURE

- ☐ 1. EXFOLIATIVE
- ☐ 2. ABRASIVE
- ____ 3.
- ____ 4.
- ____ 5.
- ____ 6.
- ____ 7.

XI CELL TYPES

- ☐ 1. SQUAMOUS
- ☐ 2. COLUMNAR
- ☐ 3. SPINDLE CELLS
- ☐ 4. TRANSITIONAL
- ____ 5. CILIATED CELLS
- ____ 6. MESOTHELIAL
- ____ 7. LYMPHOCYTES
- ____ 8. MIXED
- ____ 9. HISTIOCYTES
- ____ 10. LEUCOCYTES
- ____ 11. RED BLOOD CELLS
- ____ 12. BACTERIA
- ____ 13. OTHER CELLS

XII CELL MORPHOLOGY

- ☐ 1. ANISOKARYOSIS
- ☐ 2. NUCLEAR CYTOPLASMIC RATIO ABOVE NORMAL
- ☐ 3. HYPERCHROMASIA - RELATIVE
- ☐ 4. HYPERCHROMASIA - TRUE
- ☐ 5. PYKNOSIS
- ☐ 6. MULTI-NUCLEATION
- ☐ 7. MITOSIS
- ☐ 8. STRIPPED NUCLEI
- ☐ 9. SQUAMOUS CELL DYSKARYOSIS
- ____ 10. ANISOCYTOSIS
- ____ 11. CYTOPLASM - DECREASED; RATIO INCREASED
- ____ 12. CYTOPLASM - INCREASED
- ____ 13. MACRO NUCLEI
- ____ 14. HYPERCHROMASIA - TINCTORIAL
- ____ 15. CONDENSATION MEMBRANE
- ____ 16. NUCLEOLI - NORMAL
- ____ 17. NUCLEOLI - ENLARGED
- ____ 18. KARYOSOMES
- ____ 19. KARYORRHEXIS
- ____ 20. VACUOLIZATION OF CYTOPLASM
- ____ 21. VACUOLIZATION OF NUCLEUS
- ____ 22. KERATINIZATION
- ____ 23. PEARL FORMAT

XIII CELL MEASUREMENTS: (MEAN ± S.D. NUMBER OF CELLS MEASURED)

	MEASUREMENT	CODE
1. DIAMETER OF CELL		
2. DIAMETER OF NUCLEUS		
3. THICKNESS OF NUCLEAR BORDER		
4. DIAMETER OF NUCLEOLUS		
5. DIAMETER OF KARYOSOMES		
6. DIAMETER OF VACUOLES		
7. NUCLEAR DENSITY		

OTHER NOTES:

CYTO TEST PROCED | CELL TYPES | CELL MORPHOLOGY | SPARES | DIAMETER OF CELL | DIAMETER OF NUCLEUS | THICKNESS OF NUCLEAR BORDER | DIAMETER OF NUCLEOLUS | DIAMETER KARYOSOMES | DIAMETER OF VACUOLES | NUCLEAR DENSITY

OLLE KJELLGREN, GÖTEBORG, SWEDEN

CYTOLOGISKA LABORATORIET
Jubileumskliniken
Sahlgrenska sjukhuset
Göteborg

CYTOLOGISK UNDERSÖKNING | Lab. nr

Svaret skall sändas under adress

Född år månad dag | Patientens namn eller initialer

Identification of patient

Name of doctor

Journal nummer	Klinisk avd.	Obj.glas-nr	Provtagningsdag
Record no.	Dept.	Slide no.	Date of exam.

Provet utgöres av: Kind of smear

Prov taget med: taken with — ☐ pipett ☐ spatel från ☐ vagina ☐ cervix

Undersökningen skall debiteras

CYTOLOGISKA LABORATORIETS SVAR

☐ Normala — av. strålförändrade — celler. Normal cytology (Radiation changes)

☐ Atypiska celler närvarande. Atypical cytology

☐ Celler, sannolikt härrörande från malign vävnad, närvarande. Cytology suggestive of, but not conclusive for, malignancy.

☐ Celler från malign vävnad närvarande. Malignant cells present.

☐ Tekniskt otillfredsställande preparat. Technically unsatisfactory smear.

Description. Diagnosis and so on.

Göteborg den / —

CYTOLOGISKA LABORATORIET
Jubileumskliniken
Sahlgrenska sjukhuset
Göteborg

CYTOLOGISK UNDERSÖKNING | Lab. nr

Svaret skall sändas under adress

Född år månad dag | Patientens namn eller initialer

Identification of patient

Name of doctor

Journal nummer	Klinisk avd.	Obj.glas-nr	Provtagningsdag
Record no.	Dept.	Slide no.	Date of exam.

Provet utgöres av: Kind of smear

Prov taget med: taken with — ☐ pipett ☐ spatel från ☐ vagina ☐ cervix

Undersökningen skall debiteras

Bortlag kartongpappret vid insändandet till laboratoriet. Ni erhåller vårt svar på kopian.

Diagnos — kliniska data — frågeställning — tidigare undersöknings lab. nr

Clinical data

Sista mens. den / — Last period

Hormonbehandling? ☐ nej ☐ ja, enl. ovan Hormone Treatment?

Gyn. strålbehandling? ☐ nej ☐ ja, enl. ovan Irradiation?

Rem. läkares namn

Den / 195 Signature

Laboratoriets anteckningar

Lab. report

GSD 4.22 ↑ 11.56. 2000 2XA5 Älvsborg

LEOPOLD G. KOSS, NEW YORK,
NEW YORK, U.S.A.

PLEASE CHECK (√)

Private	
Semi P.	
Ward	
Clinic	
E C G	
Strang	
J. Ewing	
Employee	
P O P	

CYTOLOGY REQUISITION

MEMORIAL CENTER

TEL. EXT. 750

Date.....

Service.....

For Laboratory use only—Charge No.....

Stamp or PRINT name, address or room number, and chart number in this box.

Specimen submitted by Dr.....

First Smear ☐ Repeat Smear ☐ Submitted Slide ☐ Research ☐ Previous Cytology No. .....

Identity of Specimen:

SMEARS (Specify Exact Origin)
FIX IMMEDIATELY IN ETHER-ALCOHOL MIXTURE

Gyn ☐.....
Breast ☐.....
Prostate ☐
Miscellaneous ☐.....

FLUIDS (Specify Exact Origin)
ADD ALCOHOL IMMEDIATELY IN PROPER CONCENTRATION

Washings ☐.....
Sputum ☐
Body Cavities Fluids ☐.....
Urine ☐ (How Obtained) .....
Miscellaneous ☐.....

PERTINENT CLINICAL DATA Patient's Age.....

For GYN Smears Only

L. M. P. .....
OBS. data .....

	Yes	No	
Trichomonas	☐	☐	.....
Radiation	☐	☐	.....
Cautery	☐	☐	.....
Other Treatment	☐	☐	.....

Clinical Diagnosis and Findings.....
.....
.....

For All Other Specimens

Disposition of report.....

CYTOLOGY REPORT

Accession date ..... Cytology No. .....

Microscopic findings and diagnosis by Dr. ..... Date .....

Assay Malignant ☐ Suspicious ☐ Benign ☐

CYT. Report 24

JULIETA C. de LAGUNA, MEXICO, D. F., MEXICO

Department of Public Health

Gynecological Cancer

CYTOLOGICAL STUDY Record No. _____

Name _____ Lab. No. _____

Age _____ Date _____ Sent by Doctor _____

Specimens: Vaginal: Cervical: Endocervical: Endometrial: Others:

Clinical diagnosis (provisional): _____

Cellular findings: _____

Cytological diagnosis: _____

Suggestions: _____

Date: _____ Interpreted by _____

CLINICAL DATA

Date of L. M. P. _____ Length of cycle _____

Amenorrhea (cause _____

Leukorrhea Bloody discharge Metrorrhagia Menorrhagia

Cervical erosion Ulceration Ectropion Cervical tumor

Tumor of the corpus Vaginal lesion Vular lesion

Hormone therapy _____

Surgical treatment _____ Date: _____

Radiation therapy: _____

Other treatments _____

Present status _____

COMMENTS BY DOCTOR de LAGUNA:

Emphasis is placed on the fact that without clinical data, especially in functional cytological work, the cytologist is only able to provide a mere description of findings but unable to make a proper interpretation for the clinician.

In cancer diagnosis clinical data are useful as a check of the results and to depict any discrepancy between the clinical and the cytological findings. Cancer investigation is never omitted and each smear is classified accordingly. Similarly in diagnostic studies, a brief statement of the functional status is always given.

The functional aspects of reports are made in the following order:

1) Normal functional picture. We refer to the estrogenic action based on cornification due to maturation of the epithelium. It is stated when it is compatible with age and menstrual history.

2) If the functional picture is imcompatible with age or the menstrual cycle, an approximate statement of estrogenic activity is added. The report is made in arbitrary terms:
   5/5: normal average in ovulatory phase
   3/5 to 5/5: normal cycle
   2/5: hypoestrogenism
   1/5: marked hypoestrogenism
   0: absence of estrogenic action
   Hyperestrogenism: high levels out of proportion in comparison with age and cycle.

The serial studies covering cycles are accompanied with graphs.

I. First a short report on the above points is made. Example: "normal functional picture," "hyperestrogenis," "pregnancy picture," etc.

II. In the second place we refer to the elements of inflammatory reaction, Trichomonas, bacteria, cytolysis, etc. We report from + to ++++.

III. In the cytological report to the clinician we do not describe cellular changes as such but actually refer to the direct interpretation of findings. We generally follow Papanicolaou's classification, with minor changes in the intermediate groups:

Negative

Class I No cellular change (beside inflammatory reaction).
Class II Mostly inflammatory changes.
Class III More marked changes, but belonging, nevertheless, to reversible alterations: "superficial dyskaryosis," some metaplasias, hyperplasias, basal hyperactivity, "precancer cell complex of Ayre."

Positive

Class IV
Class V Papanicolaou's definition

Whenever we find Class III or IV cells, and we do not feel sure about the reversibility of the lesion, at the moment of the study, we label them Doubtful III or IV.

When possible, in addition to the cytological study proper and the classification of the degree of cellular changes, we try to recognize the original lesion. For instance, Class III cells which show basal hyperactivity, Negative II. Class II cells with changes commonly associated with Trichomonas, Negative II, etc.

In positive smears we routinely state the type of carcinoma (Grades I to IV of differentiation) or adenocarcinoma. If it applies, we state the possible presence of adenoacanthoma. RR cells and SR cells are especially reported in patients with a history of cancer.

FRANTIŠEK LUKSCH, PRAGUE, CZECHOSLOVAKIA

GYNAEKOLOGICKÉ ODD. VÚE - PRAHA: CYTOLOGICKÁ LABORATOŘ

Jméno:..... nar.....

Klin. DG:.....

.....

Kons. vyš.	Serie	Chor. č. Prep. č.	Dat. odb.
Vag.	Ektoc.	/	
Endoc.	Endom.		
Prep. č.			19

Mop	0	I	II	III	IV	V	IV	Nezpůsobilý roztěr			
Or. vyš.	Cyt. odn.	Cytol. neodp.	Estr. 0	Estr. ↑	Estr. ↑↑	Prog. 0	Prog. ↑	Prog?	Andr. ↑	Grav.?	Menop.
Or. cytogr.	4	4 -3	3 4	3	3--2	2--3	2	2 1	1- 2	1	
Cytogram	a. Bas.	b. Interm.	c. povrch	d. zroh. p.	I. Kp.	I. a.	I. c.	Leuko.	Ery.	Cyto-lysa	Hlen
	A	B	C	D	E		a	b	c	d	e
Karyom.	3	4	5	6	7	8	9	10	11	12	13
	14	15	16	17	18	19	20	21	22	23	24
Mack	I	II	III	IV	Karcinom				Neg	Susp	Pos
Barvení:								Fixace		A./E.	Nefix.
Poznámka:											

Chmo 02 - 3469 - 57

GYNECOLOGICAL DEPT. - PRAGUE: CYTOLOGICAL LABORATORY

NAME: **DATE of BIRTH:**

CLINICAL DIAGNOSIS:

Consult	Routine	UNIT NO. No. of Spec.	DATE
Vaginal	Ectoc.	/	
Endoc.	Endom.		
Cytology Number			19

Vaginal Flora	No Bacteria	Bac. Vaginalis	Mixed Flora No Leuko-cytes	Mixed Flora Plus Leuko-cytes	Gonorrhea	Trichom.	Fungi	INADEQUATE SMEAR			
Hormonal Classifi-cation	Compatible with History	In-Compatible with History	Estrogen 0	Estrogen +	Estrogen ++	Prog. 0	Prog. +	Prog. ?	Androgen +	Pregnancy ?	Meno-pause
Rough Hormonal Cytogram*	4	4 - 3	3 - 4	3	3 - 2	2 - 3	2	2 - 1	1 - 2	1	
Detailed Cytogram**	Basal	Inter-mediate	Superfi-cial Large	Superfi-cial Small	Karyopyk. Index	Acido. Index	Cornified Index	Leuko-cytes	Erythro-cytes	Cytolysis	Mu-cous
	A	B	C	D	E		a	b	c	d	e
Karyometry ( )	3	4	5	6	7	8	9	10	11	12	13
	14	15	16	17	18	19	20	21	22	23	24
Glycogen Index (Mack)	I	II	III	IV	READING FOR MALIGNANCY				Negative	Susp.	Pos-itive
Type of Staining							Type of Fixation		Alcohol Ether	Not Fixed	
REMARKS											

*Schmitt, A.: In Gynaekologische Zytologie, ed. by H. Runge. Dresden: Steinkopff pp. 15-19, 1954.
**Wied, G. L.: Am. J. Clin. Path. 25: 742-750, July, 1955.

HERBERT E. NIEBURGS, NEW YORK, NEW YORK, U.S.A.

Slide No..... **CYTOLOGY REQUEST AND REPORT** Date.....

Type of Specimen.....Name.....Age.....Race.....

Address.....Chief Complaint.....LMP.....

Doctor.....Hosp. or Office No.....Prev. Cyt. and Path. reports.....

.....Clinical diagnosis.....

Treatment, past, esp. hormones and radiation.....

☛ *Indicate Site, Method of Cell Collection and Fixation!*

A. **METHOD OF FIXATION —** (A1) Equal volumes of 95% alcohol, (A2) 70% alcohol, (A3) 50% alcohol, (A4) Mixture equal parts 95% alcohol & ether, (A5) 10% Formalin, (A6) Dried in air.

B. **ORAL CAVITY** — Surface scraping — A4 (1) Sponge biopsy — A5 (2).

C. **LARYNX** — A4 Aspiration (1) Abrasive technic (2)

D. **MAXILLARY SINUSES** — Saline irrigation — A1 (1) Smears in — A4 (2).

E. **LUNGS** — Sputum, (deep cough, fresh specimen) — A2 (1) Bronchial secretion, smears — A4 (2) Bronchial aspiration, smears — A4 (3).

F. **ESOPHAGUS** — Smears in A4 (1) Washings — A1 (2) Aspiration (3) Abrasion (4).

G. **STOMACH** — Smears — A4 (1) Washings A1 (2) Balloon (3) Brush (4) Others (5).....

H. **DUODENAL DRAINAGE** — Collect on ice and prepare smears within 10 min. Fix A4 (1).

I. **DESCENDING COLON** (1) **RECTUM** (2): Smears in A4 (3) Washings (add 10 drops of egg-albumin to each 100 cc prior to centrifugation — A1 (4) Aspiration (5) Surface abrasion (6).

J. **VULVA** — Scraping — A4 (1).

K. **VAGINA** — A6 — Aspiration (1) Cotton swab from mid-vagina (2) Request hormonal evaluation (3).

L. **CERVIX UTERI** — A6 — Aspiration post fornix (1) Swab post. fornix (2) Aspiration cervical os (3) Endocervical swab smear (4) Spatula (5) Tampon (6).
Request evaluation of sensitization response — **SR** — (7) Radiation response — **RR** (8).

M. **ENDOMETRIUM** —A4 or A6 — Aspiration (1) Abrasive methods (2).

N. **BREAST** — A4 or A6 — Secretion obtained by massage (1) Pump (2) Needle aspiration (3).

O. **SEROUS EFFUSIONS** — A3 — Pleural fluid (1) Peritoneal fluid (2) Pericardial fluid (3) Cerebrospinal fluid (4).

P. **URINE** — A1 (1) or Formalin 10 cc to each 90 cc of urine (2) Smears A4 (3).

Q. **PROSTATE** — A4 or A6 — Massage (1) Urine voided following massage A1 or P2 (2).

R. **SKIN** — A4 — Surface scrapings (1) Tissue puncture (2).

S. **TISSUE IMPRINTS** — A2 (Allow edges to dry before fixation) Specify.....

MICROSCOPIC EVALUATION

T. **CONTENTS** — Squamous (1) C(a) S(b) I(c) P(d) Columnar (2) 'non-ciliated (a) ciliated (b), Transitional (3) Goblet (4) Mesothelial (5) Origin of cells 1-5..... Lymphocytes (6) Histiocytes (7) Leucocytes (8) RBC (9) Doederlein bacilli (10) Trichomonas (11) Monilia (12) Leptothrix vaginalis (13) Coccoid bacteria (14) Organisms not identified (15) Others (16).....

CELLULAR CHANGES —

Anisocytosis (14) Anisokaryosis (15) Macronuclei (16) Increased nucl.-cytopl. ratio (17) Hyperchromasia (18) Incr. nucl. border (19) Karyosomes (20) Macronucleoli (21) Pyknosis (22) Karyorrhexis (23) Multinucleation (24) Vacuolation (25) Nucl. (a) Cytopl (b) Keratinization (26) Pearl formation (27) Mitosis (28) Cytolysis (29) Stripped nuclei (30) **SR** (31) Marked (a) moderate (b) poor (c) **RR** (32) marked (a) moderate (b) poor (c).

CYTOLOGY REPORT

U. **NO CANCER CELLS FOUND** (1) Specimen does not contain material from..... and should be therefore regarded as unsatisfactory (2).

V. **BENIGN CELLULAR CHANGES** — apparently due to: Hyperplasia (1) Squamous metaplasia (2) Inflammation (3) Polyp (4) Atypical hyperplasia slight (a) mod. (b) Other (5).....

W. **MALIGNANT CELLULAR CHANGES** — Specify — Type (1)..... Grade (2)..... Site (3)..... Origin (4).....

X. **EQUIVOCAL CELLULAR CHANGES** — of borderline type (1).....Unknown type (2) due to unsatisfactory specimen (3). Evaluation deferred until examination of repeat specimens (4).

Y. **RECOMMENDATIONS:** — Repeat examination — immediately (1) Frequently (2) Months 1 (3) 3 (4) 6 (5) 12 (6). Following therapy (7) specify..... Observe proper instructions (8) for cell collection (a) preparation (b) fixation (c) Take specimen from (9)..... Obtain final diagnosis by procedures other than cytology (10). Specify.....

Z. **HORMONAL EVALUATION OF VAGINAL SMEARS** — Suggestive of (1) Indicative of (2) Comparable to (3) Post ovulatory phase (4) Proliferative phase (5) Early (6) Late (7) Non ovulatory cycle (8) Secretory phase (9) No evidence of ovulation prior to smear (10) Estrogen deficiency (11) Slight (12) Moderate (13) Marked (14) Apparently adequate estrogen activity (15) Increased estrogen activity (16) Possibly previous non ovulatory cycle (17) Normal hormone levels during pregnancy (18) Progesterone deficiency (19) Slight (20) Moderate (21) Marked (22) Impending abortion (23) May normally occur at 3rd month of pregnancy (24). Non specific smear due to excessive cytolysis (25). If hormonal evaluation desired, repeat following alkaline douches (26). Post partum: During lactation (27) Not lactating (28) Normal (29) Abnormal (30) Re-established estrogenic function: Slight (31) Moderate (32) Marked (33). Continued estrogenic stimulation unopposed by episodes of progesterone activity (34). Protracted estrogen activity, possibly slightly decreased (35).

COMMENTS:

Signed.....
Dr. H. E. Nieburgs

GEORGE N. PAPANICOLAOU,
NEW YORK, NEW YORK, U.S.A.

PRIVATE AMBULATORY PATIENTS

REQUEST FOR CYTOLOGIC DIAGNOSTIC STUDY BY THE PAPANICOLAOU CYTOLOGY LABORATORY

DEPARTMENT OF PATHOLOGY, THE NEW YORK HOSPITAL – CORNELL MEDICAL CENTER, 1300 YORK AVENUE, NEW YORK 21, N. Y.

CYTOLOGY NUMBER _____ | N. Y. HOSP. HIST. NO. _____ | BILL SHOULD BE SENT TO: PATIENT ☐ DOCTOR ☐ | DATE OF SPEC. _____

PRINT PATIENT'S NAME AND ADDRESS

PRINT DOCTOR'S NAME AND ADDRESS

DO NOT WRITE IN THIS SPACE – PLEASE REMOVE CARBON PAPER BEFORE SENDING TO LABORATORY

SEND SPECIMENS TO ROOM A-128 BEFORE 4 P.M. (MON. - FRI.); 11 A.M. (SATURDAY)

BE SURE TO LABEL ALL SPECIMENS AND SMEARS WITH PATIENT'S NAME AND SOURCE OF MATERIAL.
SEE MIMEOGRAPHED INSTRUCTIONS FOR PROPER PROCEDURES FOR THE COLLECTION AND FIXATION OF SPECIMENS.

CHECK TYPE OF SPECIMEN SUBMITTED:

GYN.: VAGINAL_____ CERVICAL_____ ENDOCERVICAL_____ ENDOMETRIAL_____

PULM.: SPUTUM_____ BRONCHIAL ASP. RT._____ LEFT_____ BRONCH. WASH. RT._____ LEFT_____

G-U: VOIDED URINE_____ CATH. URINE_____ URETERAL RT._____ URETERAL LEFT._____

VOIDED AFTER PROST. MASSAGE_____ PROSTATIC FLUID_____ PROSTATIC SMEAR_____

G-I: ESOPH. ASP._____ WASH._____ GASTRIC ASP._____ DUOD. DR._____ COLON. WASH._____ RECTAL WASH._____

EXUDATES: PLEURAL_____ PERITONEAL_____ PERICARDIAL_____

OTHER SPECIMENS (SPECIFY TYPE):

HISTORY (TO BE FILLED IN FOR ALL TYPES OF SPECIMENS)

AGE_____ SEX: M._____ F._____

X-RAY THERAPY: YES_____ NO_____ (HOW RECENT?)

HORMONAL THERAPY: YES_____ NO_____ (HOW RECENT?)

PROVISIONAL DIAGNOSIS:

PLEASE MENTION FINDINGS FROM X-RAY, CYSTOSCOPY, BRONCHOSCOPY, BIOPSY, ETC., WHICH SUGGEST THE POSSIBILITY OF TUMOR:

ADDITIONAL INFORMATION REQUESTED FOR GYNECOLOGICAL SMEAR STUDY

L. M. P.: OTHER BLEEDING:

MARITAL CONDITION: S. M. W. D.

CHIEF COMPLAINTS:

RECENT CAUTERIZATION? DATE:

PELVIC EXAMINATION:

GYN. OPERATIONS INCLUDING D & C, BIOPSIES, DATES:

REMARKS:

SPECIMENS WILL NOT BE EXAMINED UNLESS ACCOMPANIED BY THIS FORM, PROPERLY FILLED OUT

HANNAH PETERS, BOMBAY, INDIA

CYTOLOGY LABORATORY

INDIAN CANCER SOCIETY
Tel. No. 60051-52.

TATA MEMORIAL HOSPITAL,
Hospital Avenue, Parel, Bombay.

CYTOLOGICAL EXAMINATION FOR MALIGNANCY

Patient's Name ..... Age .....

Hindu..... Deccani / Gujrati Mohamedan ..... Parsi ..... Christian ..... Jew ..... Other .....

Address ..... Case No. .....

Source of specimen : Cervix ..... Vagina ..... Other .....

Date of Collection ..... Biopsy taken : Yes ..... No ..... Date ..... Path. No. .....

Date of onset of last menstrual period .....

Has Patient Received Estrogen Therapy : Yes ..... No .....

Estrogen Therapy Started : Date ..... Ended .....

Has Patient Received Radiation Therapy : Yes ..... No. .....

Deep X-Ray : Date from ..... To .....

Radium : Dates .....

Clinical Diagnosis .....

Remarks .....

Physician's Name .....

Address ..... Tel. No. .....

Lab. No. ..... Examined By ..... Date Reported .....

INDIAN CANCER SOCIETY **CYTOLOGY LABORATORY** Tata Memorial Hospital
Hospital Avenue, Parel, Bombay.

CYTOLOGICAL EXAMINATION FOR MALIGNANCY

Patient's Name .....

Address ..... Case No. .....

Source of Specimen : Cervix ..... Vagina ..... Other .....

Date of Collection: ..... Cytology No. .....

Physician's Name .....

CYTOLOGICAL INTERPRETATION

Date of Report *Signature.*

JAMES W. REAGAN, CLEVELAND, OHIO, U.S.A.

REQUISITION FOR CELLULAR EXAMINATION

DATE _____ L.M.P. _____ LABORATORY NO. _____

CERV. ASP. ☐ CERV. SCRAP. ☐ VAGINAL ☐ OTHER ☐ _____

PATIENT'S NAME _____ AGE _____

WHITE ☐ NON-WHITE ☐ CLIN. DX _____

SYMPTOMS: NONE ☐ ABNORMAL VAG. BLEEDING ☐ _____

CERVIX: NEG. ☐ EROSION ☐ CERVICITIS ☐ ?CA ☐ CA ☐ STAGE _____

PAST UTERINE RX: NONE ☐ IRRADIATION ☐ ESTROGEN ☐ _____

PREVIOUS STUDIES: CYTOLOGY ☐ NO ☐ YES BIOPSY ☐ NO ☐ YES

SEND REPORT TO FOLLOWING PHYSICIAN:

FOR REPORTING. DO NOT WRITE HERE.

☐ CELL STUDY NEGATIVE. REPEAT IN 1 YR.

☐ CELL STUDY UNSATISFACTORY BECAUSE OF _____

☐ REPEAT CELLULAR STUDIES IN THIS CASE IN

☐ MONTHS OR

☐ AT ONCE

☐ CELLULAR STUDY INDICATES NEED FOR FURTHER DIAGNOSTIC STUDY. IT IS GENERALLY ACCEPTED THAT STUDIES INCLUDE

☐ PUNCH BIOPSIES

☐ CONIZATION

☐ CURETTAGE

CELLULAR CHANGES: _____

SIGNED: _____ M.D.

THOMAS R. SIMON, OMAHA, NEBRASKA, U.S.A.

CREIGHTON UNIVERSITY SCHOOL OF MEDICINE

Gynecological Cancer Detection Clinic

Date _____ Cytology Lab. No. _____

NAME OF PATIENT _____ RACE _____ AGE _____

ADDRESS _____ Dispensary Chart No. _____

SOURCE OF SMEARS: Check below please

- Aspiration posterior fornix _____
- Aspiration cervical os _____
- Aspiration cervical canal _____
- Cervical scraping _____
- Fundus _____
- Sounding _____

CHECK PURPOSE OF THIS TEST:

- Initial examination _____
- Recheck _____
- Radiation reaction _____
- Recurrency _____

HISTORY OF PATIENT: Married _____ Single _____

Date of L. M. P. _____ or Date of Menopause _____

Para _____ Gravida _____

HISTORY OF ANY ABNORMAL BLEEDING:

HISTORY OF ANY ABNORMAL DISCHARGE:

PREVIOUS GYNECOLOGICAL SURGERY AND BIOPSY OR D & C DIAGNOSIS:

PREVIOUS OR PRESENT ESTROGENIC THERAPY:

HISTORY OF FAMILIAL CANCER:

X-RAY OR RADIUM PREVIOUS OR PRESENT, WITH DATES AND NUMBER OF TOTAL DOSAGE OF BOTH RADIUM AND X-RAY:

DOUCHES: Routine _____ Occasional _____ Date of last douche _____

REMARKS AND CLINICAL FINDINGS:

Signed _____ Staff physician

Signed _____ Clinical clerk

CLASSIFICATION OF CERVICAL CYTOLOGY SMEARS

Class

I. Negative, including inflammation atypia.
II. Atypia, of questionable significance but short or suspicious for Carcinoma. Repeat within 6 months is indicated.
III. Suspicious for Carcinoma.
IV. Positive for Carcinoma, probably in Situ.
V. Positive for Carcinoma, probably invasive.

Immediate repeat and biopsy are indicated for those who fall under Class III, IV, and V.

T. Simon, M. D.
Pathology Department

PETER STOLL, HEIDELBERG, GERMANY

Von Station: _____

(Name, Vorname, Alter)

L. Regel: Menop. seit: Ausfallersch.:

Hormone: Bestrahlung:

Fragestellung: smear:

indirekt: ○ Funktion ○ Gravidität direkt: ○ Erosion ○ Erosion susp. ○ Carcinom

Klin. Diagnose:

Frühere U. No.:

Cytologischer Befund:

Pl. Ep.	normal a	normal b	abnorm a	abnorm b	atypisch a	atypisch b
5						
4						
3						
2						
1						
n. Kern						
Cervix						
Korpus						

Ery: Leuko: Histio: Dö: Bakt: Trichom: Pilz

Reinheitsgrad (1) (2) (3)

Op. Fu. Cy.

Proliferation:
1. sehr hoch (oestrogen)
2. hoch (oestrogen)
3. fehlt (funktionslos)
4. mittel (ev. Progesteron)
5. Mischtyp
6. mittel (ev. Androgen)
7. mittel (ev. Gravidität)
8. fehlt (Atrophie)

Lokal:
1. Erosionszellen (Plattenepithel)
2. Erosionszellen (Zylinderep.)
3. Entzündung
4. Blutung
5. Punktat
6. Aspiration
7. Urin
8. Sonstiges

Carcinom:
1. negativ (Pap. I u. II)
2. Wiederh. (Pap. III)
3. positiv (Pap. IV u. V)
4. bestrahlt negativ
5. bestrahlt Wiederh.
6. bestrahlt positiv

9. ungenügend

An Station:

Op. Fu. Cy.

(Name)

smear direkt indirekt

Proliferation:
1. sehr hoch (oestrogen)
2. hoch (oestrogen)
3. fehlt (funktionslos)
4. mittel (ev. Progesteron)
5. Mischtyp
6. mittel (ev. Androgen)
7. mittel (ev. Gravidität)
8. fehlt (Atrophie)

Lokal:
1. Erosionszellen (Plattenepithel)
2. Erosionszellen (Zylinderep.)
3. Entzündung
4. Blutung
5. Punktat
6. Aspiration
7. Urin
8. Sonstiges

Reinheitsgrad (1) (2) (3)

Carcinom:
1. negativ (Pap. I u. II)
2. Wiederholung (Pap. III)
3. positiv (Pap. IV u. V)
4. bestrahlt negativ
5. bestrahlt Wiederholung
6. bestrahlt positiv

Empfehlung:

9. ungenügend Datum: Signum:

FROM WARD: _____

(name, first name, age)

LMP: Menopause since:

Climacteric syndrome:

Hormones: Irradiation:

QUESTION: smear:

indirect: direct:

○ ovarian function ○ erosion

○ pregnancy ○ suspicious erosion

○ carcinoma

CLINICAL DIAGNOSIS:

PREVIOUS UNIT NO:

CYTOLOGICAL READING:

SQUAMOUS EPITHELIUM	NORMAL a	NORMAL b	ABNORMAL a	ABNORMAL b	ATYPICAL a	ATYPICAL b
5						
4						
3						
2						
1						
free nuclei						
endocervix						
intrauterine						

erythro: leuko: histio: B vag: mixed bact:

Op. Fu. Cy.

Trichom: fungi: degrees of Döderlein: (1) (2) (3)

PROLIFERATION:
1. very marked (estrogenic)
2. marked (estrogenic)
3. none (no ovarian function)
4. intermed. (prob. progestogenic)
5. mixed type
6. intermed. (prob. androgenic)
7. intermed. (prob. pregnant)
8. none (atrophy)

LOCAL:
1. erosion (squamous cells)
2. erosion (cylindric cells)
3. inflammatory reaction
4. bleeding
5. paracentesis
6. aspiration
7. urine
8. misc.

CARCINOMA:
1. neg. (Pap. Class I & II)
2. repeat (Pap. Class III)
3. positive (Pap. Class IV & V)
4. irradiated neg.
5. irradiated repeat
6. irradiated positive

9. inadequate

TO WARD: _____

(name)

Op. Fu. Cy.

smear direct indirect

PROLIFERATION:
1. very marked (estrogenic)
2. marked (estrogenic)
3. none (no ovarian function)
4. intermed. (prob. progestogenic)
5. mixed type
6. intermed. (prob. androgenic)
7. intermed. (prob. pregnant)
8. none(atrophy)

LOCAL:
1. erosion (squamous cells)
2. erosion (cylindric cells)
3. inflammatory reaction
4. bleeding
5. paracentesis
6. aspiration
7. urine
8. misc.

degrees of Döderlein: (1) (2) (3)

CARCINOMA
1. neg. (Pap. Class I & II)
2. repeat (Pap. Class III)
3. positive (Pap. Class IV & V)
4. irradiated neg.
5. irradiated repeat
6. irradiated positive

RECOMMENDATION:

9. inadequate

date: signature:

We proceed as follows (scheme of out-patient department examination)

1. The patient is put on the examining table, and the uterine cervix is visualized and inspected.

2. Secretions from the vaginal fornix are taken by means of a platinum loop and examined immediately under the phase microscope. These findings are recorded in pencil.

3. The findings of the routine colposcopic examination are also marked on the accompanying sheet.

4. Cervical and endocervical smears are prepared by means of cotton applicators and fixed in alcohol-ether. The examination of these smears is done after staining in the cytology laboratory. These findings are recorded with ink and compared with the phase contrast findings (previously marked in pencil).

5. Routine gynecological examination (with biopsy if necessary).

In addition to the routine clinical information which may be seen on the enclosed sheet, we find it advantageous that the clinician ask specific questions which require special consideration, such as "Are the cytological findings compatible with the menstrual history?" or "Is the present erosion cytologically suspicious?"

Another important factor in our examinations is that we require that the clinician, who sees the patient and who examines the fresh smear under the phase microscope in the out-patient department, also see the fixed and stained smear (with the consultation of the cytologist-in-charge) - in the cytology laboratory.

The findings are then marked in the scheme in the center of our accompanying sheet. We estimate as closely as possible the relative amount of the various cell types of squamous cells, making a dash for every 10 cells in the respective area of the scheme. "A" and "B" stand for acidophilic and basophilic respectively.

The final evaluation is made by an experienced cytologist, who marks the answers on the accompanying sheet.

The right portion of the sheet is returned to the ward or out-patient department, containing the recommendations for further therapeutic or diagnostic procedures (such as treatment of infection, repeat smear, biopsy). The statistical evaluations of our findings are done by means of a regular IBM system (Hollerit - Key).

GUILLERMO TERZANO, BUENOS AIRES, ARGENTINA

NAME OF THE PATIENT:

AGE: **CHILDREN:** **ABORTIONS:**

L. M. P.:

CHIEF COMPLAINTS:

GYNECOLOGICAL FINDINGS:

PREVIOUS TREATMENT:

COLPOSCOPY (date):

CYTOLOGY (date):

DIAGNOSIS: CLINICAL:

PATHOLOGICAL:

CYTOLOGICAL REPORT

1. **Technique used for the taking of the specimens:**

   Vaginal Aspiration
   Cervical Aspiration
   Cervical Scrapings
   Endometrial Aspiration
   Endometrial Brush

2. **Staining:** **Papanicolaou**
   Shorr

3. **Trophism**
   % of each cell type

4. **Description of the vaginal smear:**

   Leukocytes
   RBCs (if any)
   Parasites (if present)
   Histiocytes
   Pattern of the smear: **follicular phase**
   luteal phase

5. **Ectocervical cytology**
   Endocervical cytology
   Endometrial cytology

6. **Cytological Diagnosis:**

GEORGE L. WIED, CHICAGO, ILLINOIS, U.S.A.

DO NOT FOLD THIS FORM

Please write firmly or use stamping machine. This is a MULTIPLE FORM.

Specimens will not be examined unless accompanied by this form, properly and legibly filled out.

The Chicago Lying-in Hospital and Dispensary

LABORATORY OF EXFOLIATIVE CYTOLOGY

Unit No.

Name

THE UNIVERSITY OF CHICAGO CLINICS

Clinic or Floor | Date

CYTOLOGICAL EVALUATION:
(To be filled out by cytology)

(I) CANCER READING

SQUAMOUS CELLS

- ☐ (0) No reading given. See remarks or Key.
- ☐ (1) Present material negative.
- ☐ (2) Apparently benign changes (negative).
- ☐ (3) Suggestive of malignancy (suspicious).
- ☐ (4) Highly suggestive of malignancy (positive).
- ☐ (5) Conclusive for malignancy (positive).

GLANDULAR CELLS

CYTOLOGY No. V-5 - (15-22)

(II) INFLAMMATORY REACTION PRESENT: Yes ☐ No ☐ ☐ VAGINA

IF ANY, THE SITE OF INFLAMMATORY REACTION SEEMS TO BE IN THE ☐ CERVIX (39)

THE INFLAMMATORY REACTION IS APPARENTLY: ☐ MILD, ☐ MARKED ☐ ENDOCERVIX

(III) THE VAGINAL FLORA CONSISTS MAINLY OF: B. VAG. ☐ MIXED BACT. ☐ COCCID B. ☐ TRICH. ☐ FUNGI ☐

(IV) THE HORMONAL READING COULD BE MADE: Yes ☐ No ☐

The findings are compatible with age of patient and history: Yes ☐ No ☐ If not, see Remarks.

(V) REMARKS: Consult key for detailed information: ☐

From these cytological findings, the histological specimen is expected to show:

(23) A
(24-28) B
(29) C
(30-38) D
(40) E
(41) F
(42-44) G

DO NOT WRITE IN THIS SPACE

To: (1) FILE
(2) Chart
(3) Dr.
(4) Dr.

COLPOPHOTOGRAPHIC FINDINGS (COLPOSCOPY)

First screening
A
B
C
D
E
F
G
Remarks:

Second screening
A
B
C
D
E
F
G
Remarks:

TO BE FILLED OUT BY CLINICAL PHYSICIAN DO NOT WRITE ABOVE LINE

(46-47) AGE ____ years (48-49) REGULAR MENSTRUAL CYCLE? Yes ☐ No ☐

First day of LMP _____ First day of PMP _____

(50-52) MENOPAUSE? Yes ☐ ____ months ago ____ yrs. ago

(53-54) PREGNANT? Yes ☐ Weeks gestation _____

(55-56) POST-PARTUM? Yes ☐ Weeks after delivery _____

(57) HORMONE THERAPY? Yes ☐ Dates _____
(within last 3 months)
Type and dosages _____

(58-60) RADIATION THERAPY? Yes ☐ Dates _____
Total dosage _____

(61) PREVIOUS GYNECOLOGICAL SURGICAL THERAPY: Yes ☐

D & C ☐ Year _____ Result _____
Biopsy ☐ Year _____ Result _____
Subt. hyst. ☐ Total hyst. ☐ Wertheim ☐ Year _____
Unilateral ☐ Bilateral ☐ oophorectomy "Year _____
Others: _____

(62) REMARKS: _____

(63-64) SMEARS PREPARED BY Dr. _____
(special reports will be sent to above doctor only if smears are abnormal)

(65) GYNECOLOGICAL FINDINGS:
1. Completely negative ☐
2. Fungi ☐
3. Trichomonas ☐
4. Vaginitis ☐
5. Cervicitis ☐
6. Endocervicitis ☐
7. Erosion (appar. benign) ☐
8. Suspicious lesion ☐
9. Polyp ☐
10. Contact bleeding ☐
11. Postmenopausal bleeding ☐
12. Other _____

(66) SURGERY CONTEMPLATED: Yes ☐
D & C ☐ Approx. date: _____
Biopsy ☐ Approx. date: _____
Hyster. ☐ Approx. date: _____
Other: _____

(67-70) If smear is REPEATED include previous CYTOLOGY No. and date.
No. _____ Date _____

SEND REPORT TO:
CHART ☐ AND
Dr. _____
(Write in here name only if copy of report is requested in any case)

THE ABOVE INFORMATION IS ESSENTIAL FOR CYTOLOGICAL EVALUATION PLEASE COMPLETE

See reverse side of this sheet for technique.

The Chicago Lying-in Hospital and Dispensary

LABORATORY OF EXFOLIATIVE CYTOLOGY

Unit No.

Name

THE UNIVERSITY OF CHICAGO CLINICS

Clinic or Floor | Date

CYTOLOGY No. V-5 -

CYTOLOGICAL EVALUATION:

(To be filled out by cytology)

(I) CANCER READING

☐ (0) No reading given. See remarks or Key.

SQUAMOUS CELLS
☐ (1) Present material negative.
☐ (2) Apparently benign changes (negative).
☐ (3) Suggestive of malignancy (suspicious).
☐ (4) Highly suggestive of malignancy (positive).
☐ (5) Conclusive for malignancy (positive).

GLANDULAR CELLS
☐ ☐ ☐ ☐ ☐

(II) INFLAMMATORY REACTION PRESENT: Yes ☐ No ☐

IF ANY, THE SITE OF INFLAMMATORY REACTION SEEMS TO BE IN THE ☐ VAGINA ☐ CERVIX ☐ ENDOCERVIX

THE INFLAMMATORY REACTION IS APPARENTLY: ☐ MILD, ☐ MARKED

(III) THE VAGINAL FLORA CONSISTS MAINLY OF: B. Veg. ☐ Mixed Bact. ☐ Coccoid B. ☐ Trich. ☐ Fungi ☐

(IV) THE HORMONAL READING COULD BE MADE: Yes ☐ No ☐

The findings are compatible with age of patient and history: Yes ☐ No ☐ If not, see Remarks.

(V) REMARKS: Consult key for detailed information: ☐

From these cytological findings, the histological specimen is expected to show:

A
B
C
D
E
F
G

To: (1) FILE
(2) Chart
(3) Dr._____
(4) Dr._____

COLPOPHOTOGRAPHIC FINDINGS (COLPOSCOPY) (45):

KEY:

A. Cytological analysis on squamous carcinoma or undifferentiated cancer

0. No reading given, see remarks or key
1. Absence of atypical or abnormal cells in the present material (definitely negative)
2. Slightly atypical cytology (may be inflammatory) but no evidence of malignancy in the present material (most probably negative)
3. Cytology suggestive of, but not conclusive for, malignancy (possibly positive)
4. Cytology strongly suggestive of malignancy (positive)
5. Cytology conclusive for malignancy (squam. epith. or undiff. Ca) (positive)

B. Cytological analysis of adenocarcinoma

0. No cells found (no reading on adenocarcinoma made)
1. Normal cells found (negative)
2. Degenerated cells found (most probably negative)
3. Atypical cells found (may be positive)
4. Abnormal cells found (positive)
5. Cells found which are consistent with adenocarcinoma (positive)

C. Hormonal reading

1. Cytological findings are compatible with the age of patient and history
2. Cytological findings are incompatible with the age of patient and history
3. Marked estrogenic effect
4. Apparently slight estrogen effect
5. Marked estrogen deficiency (atrophic menopausal type)
6. Apparently menopausal smear type, but not atrophic menopausal type
7. Apparently effect of androgens
8. Apparently effect of progestational agents or corpus luteum hormone
9. Findings compatible with pregnancy
10. No hormonal reading possible from this material (see D, E or/and G)
11. The hormonal reading can be made only from a repeated study (see G)

D. Leukocytes, red blood cells and histiocytes

1. No leukocytes in (*a*) vaginal, (*b*) cervical, (*c*) endocervical smears
2. Moderate number of leukocytes found in (*a*) vaginal, (*b*) cervical, (*c*) endocervical smears
3. Abundant leukocytes found in (*a*) vaginal, (*b*) cervical, (*c*) endocervical smears
4. Well-preserved leukocytes in (*a*) vaginal, (*b*) cervical, (*c*) endocervical smears
5. Slightly degenerated leukocytes in (*a*) vaginal, (*b*) cervical, (*c*) endocervical smears
6. Markedly degenerated leukocytes in (*a*) vaginal, (*b*) cervical, (*c*) endocervical smears
7. No red blood cells found in (*a*) vaginal, (*b*) cervical, (*c*) endocervical smears
8. Red blood cells found mainly in (*a*) vaginal, (*b*) cervical, (*c*) endocervical smears
9. Histiocytes found in (*a*) vaginal, (*b*) cervical, (*c*) endocervical smears

E. Microbiological classification

1. Mainly Bacillus vaginalis (*a*) with, (*b*) without cytolysis (healthy vaginal flora)
2. Mixed bacteria
3. Mainly cocci or coccoid bacteria
4. Trichomonas vaginalis
5. Fungi
6. No visible bacteria or no bacteriological classification possible from this material

F. Radiation cell changes

1. No radiation cell changes found
2. Slight radiation cell changes found
3. Marked radiation cell changes found
4. This is only a cytomorphologic description, not a prognosis (see G10)
5. According to Graham's criteria, patient should be treated with irradiation
6. According to Graham's criteria, patient should be treated with surgery

G. Recommendation

1. Dried or insufficient material for exact reading; send more material
2. Repeat all three smears for final evaluation as soon as possible. The present reading is only informative.
3. Keep under observation, repeat smear at least quarterly.
4. Repeat smears after treatment of present infection
5. For better differentiation perform proliferation test: repeat smears 4 days after injection of 10 mg. estradiol-benzoate or 5 mg. stilbestrol, or repeat smears 2 days after an oral therapy with 1 mg. diethylstilbestrol daily through 5 days
6. Insufficient clinical information. No reading possible
7. For exact evaluation of ovarian cycle prepare daily smears through one cycle
8. Preliminary ovarian function study: prepare smears 14 and 3 days prior to next expected menstruation
9. Perform endometrial smear to rule out presence of corporal carcinoma (see No. 4 on reverse side of white sheet for instruction)
10. For cytoprognostic evaluation of radiation response: prepare smears prior to onset of therapy and daily after onset of therapy for period of 24 days
11. Histologic verification suggested
12. Colposcopy suggested

WRITE THE UNIT NUMBER ON THE LOWER PART OF FROSTED PART OF SLIDE.

Preparation of the Material

(Obstetrics and Gynecology)

The patient is placed upon an examining table in the lithotomy position. A speculum is introduced into the vagina, and the portio vaginalis uteri is visualized. The patient should not have any intravaginal examinations, douches, or therapy of any kind twenty-four hours prior to the cytological examination. If this is unavoidable, indicate so on the accompanying sheet. Lubricant should not be introduced into the vagina, as it interferes with the staining reactions. Except when the patient is a virgin or in those postradiation cases in which the introitus is stenosed and therefore a speculum cannot be inserted, it is requested that the following three types of smears be made on *one* slide:

(1) *Scrape slightly* with an ordinary wooden spatula the upper lateral wall of the vagina, and smear on the section of the slide closest to the frosted end.

(2) *Scrape slightly* with an ordinary wooden spatula the entire portio vaginalis uteri, especially the borders of an erosion, and smear on the middle section of the slide.

(3) Introduce a cotton swab applicator (preferably made wet prior to the introduction) into the cervical canal and *rotate slightly*, and smear on the section of the slide furthest from the frosted end.

(4) In special cases (suspicion of endometrial cancer) a fourth smear (endometrial aspiration) should be performed, since the above three smears usually do not contain adequate material from the uterine cavity. **A distinct percentage of endometrial carcinomas will remain undetected if intra-uterine smears are not performed.** Introduce under sterile conditions a bent, dumb canula on a glass syringe and aspirate, or use the abrasive canula with nylon fibers, and smear on a separate slide.

As soon as the smear is spread, it should be **immersed immediately** *while still wet* into a fixative solution consisting of equal parts of ether and 95 per cent ethyl alcohol. Even a moment's delay may permit the thinnest portions of the smear to dry and cause significant loss of cytological detail. Send the fixed slide to the laboratory. Minimum fixation time is 10 minutes.

Proliferation test with estrogens (G5 on diagnostic key: Repeat smears on the fourth day after injection of 10 mg. estradiol-benzoate or 5 mg. stilbestrol) is requested in those cases where either menopausal cell changes or inflammatory reactions make the proper cytological evaluation too difficult from the initial smears. The estrogens may be administered also as intravaginal suppositories or orally (see G5).

Hormonal reading of smears often requires follow-up studies. An exact evaluation of the menstrual cyclic changes can be made only from smears prepared every day through one cycle. For an informative reading in sterility cases smears should be made 14 and 3 days prior to the next expected menstruation.

Suggestive prognosis of radiation reaction can be made only from material taken shortly before and after the onset of irradiation. Smears should be made prior to radiation therapy and at least every other day during the first 24 days after onset of radiation therapy. In smears of patients who were irradiated longer than three weeks ago, the presence or absence of radiation cell changes is merely a cytomorphological report and has no prognostic significance (F4 on diagnostic key).

FOR ANY FURTHER INFORMATION

call

THE CYTOLOGY LABORATORY (MIdway 3-0800), Extension 3515

HANS KLAUS ZINSER, COLOGNE, GERMANY

F (gyn.)

Krebsberatungsstelle: | Überweis. behand Arzt/Facharzt | unters. am | Wievielte Untersuchung? | Raum für Reiter in Verdachtsfällen | Signierkästchen f. statist. Bearb. (Nicht beschr.)

Arzt:

I. Name: Wohnort: Straße:

led., verh., verw., gesch., Geburtsdatum: Kostenträger:

Beruf der Pat.: Beruf des Ehemannes:

Kommt durch: Arzt, untersuchte Fr., Fürsorgerin, Presse, Merkblätter, Vorträge, Theater, Film, Rundfunk.

„ aus: Vorsicht, Krebsangst, wegen Beschwerden.

II. Vorgeschichte: Neubildungen bei Blutsverw.:

Eigene (früh. Erkrankungen, Op.):

Zahl der Geburten: , Fehlgeburten: , Zyklus: Tage, Letzte P.:

Menopause seit: , Blutungsanomalie:

Sonstige Beschwerden (Art und Dauer):

Bitte mit deutlicher Schrift ausfüllen!

III. Befund: (Durch äußerl.-, vag./rekt-, Speculumunters.) **Nur pathol. Befunde eintragen!**

1 Extragenitaler Organbefund:

2 Mammae (Schema):

3 Abdomen:

4 Vulva:

5 Vagina:

6 Portio/Cervix:

7 Uterus:

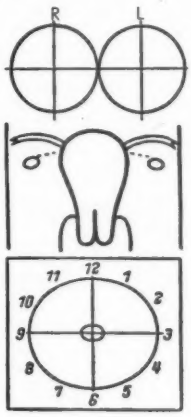
8 Adnexe:

9 Parametrien:

10 Douglas:

Jodfreier Bezirk: Ja - nein; Sondenprobe: Cytol. Unters.:

Kolposkop. U. (Schema)



IV. Diagnose: 1) o. B.

2) Behandlgsbedürftige gyn. Erkrankungen (außer Ca) an Organ (Nr.):

3) Atyp. Epithel: Leukoplakie, Grund, Felderung, uncharakt. jodfreier Bezirk

4) **Ca(-Verdacht):** neu / Rezidiv / Metastasen } an Organ ; Klärung erforderl. dch.:

Bogen erst einreichen, wenn Verdacht geklärt: falls erforderlich, Fürsorgerin einschalten!

Ca bestätigt?: Ja-nein, am ; durch:

Bei alten Ca-Fällen: 1. Behdlg. 19 , an Organ Op. -- Rad. / Rö.

V. Beratung: Wiederbestellt in Tagen, Wochen, Mon. oder sofort bei atyp. Blutung.

Dr. med. mit - ohne Benachrichtigg. zurück- / zugeschickt

Bei Ca-Befund: Behandlung eingeleitet: wo? ; am

VI. Bemerkungen: (z. B. bei Verschleppung, Behandlung durch Nichtarzt, Notwendigkeit fürsorgerischer Betreuung)

CANCER DETECTION CENTER: Doctor:	Referral by G.P./gynecologist	Examined on	How often examined	Check this space if suspicious for cancer	Do not write in this space

1. Name: Address:
single, married, widow, divorced Date of Birth: charged to:
occupation of patient: occupation of husband:
Stimulated to have examination by: doctor, social worker, leaflet, movies, radio
Because of: precautionary measure, fear of ca. symptoms

2. History: cancer of relatives:

own history (previous diseases, surgery):

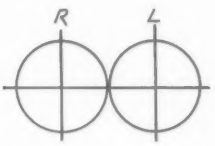
deliveries: abortions: cycle: days, L. M. P.

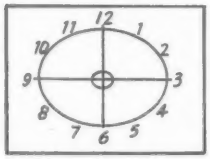
menopause since: atypical bleeding:

other symptoms (type & duration):

3. Findings: write in only pathological findings
(by external exam - vaginal/rectal - speculum)

1. extragenital organic findings:
2. breasts (scheme):
3. abdomen:
4. vulva:
5. vagina:
6. uterine cervix/endocervix:
7. uterus:
8. adnexa:
9. parametria:
10. Douglas:





iodine negative area: yes no; sound test:

cytology exam:
colposcopic exam (scheme):

4. Diagnosis: 1) normal
2) gyn. disease requiring therapy (except ca)
3) atypical epithel.: leukoplakia, ground, fielding, uncharacteristic iodine neg. area
4) ca(suspicious) new / recur / metast } on organ ; verification necessary by:

file this sheet only if suspicion verified; if nec. contact social worker

ca verified?: yes - no; date ; by:
old cancer cases: therapy 19 , on organ surg --rad/X-ray

5. Recommendations: called back in days weeks months or immediately
if atypical bleeding

Dr. sent back with-without letter; referred
In ca - diagnosis: therapy started: where? date:

6. Remarks: (e. g. unnecessary delay, therapy by non-medical person, social worker required)

A B C D E F G H IJ K L M N O PQ R S Sch T U V W XYZ

Cytologisches Zentrallaboratorium der Gesellschaft zur Bekämpfung der Krebskrankheiten Nordrhein/Westf. e.V.
(Leitung: Prof. Dr. H. K. Zinser, Köln-Lindenthal, Weyertal 76. Fernsprecher: 413477, 414121)

Lfd. Nr.

Name	Vorname	(Bei Wiederholung bitte alte Nr. angeben)
Alter	geb. am	Anschrift: (Ausfüllung nicht unbedingt erforderlich)

Jetziger mensueller Status:			Frühere Behandlungen:	
vor Menarche			Operation:	
primäre Amenorrhoe			Entfernung der Portio	
regelmäßiger Zyklus (L. Periode)			Entfernung des Uterus	
unregelmäßiger Zyklus "			Supravaginale Uterusamputation	
sekundäre Amenorrhoe "			Entfernung eines Ovars	
Menopause			Entfernung beider Ovarien	
Zahl der Geburten	Liegt jetzt Gravidität vor?	ja nein	Ra/Rö Bestrahlung:	
			Carcinom-Dosis	
Zahl der Fehlgeb.		Monat	Ra - Menolyse	
			Rö - Kastration	

Klinische Diagnose:
(einschl. Spiegelbefund)

Kolposkopie		Photo-Nr.
Datum		Photo-Nr.
Datum		Photo-Nr.

Präparat-Nr.	Grad :	Mischtyp		Kokkentyp		Dyskarios. O'Zellen	
		Mucosustyp		Doederlein		Dyskarios. tief. Zellen	
		Mangeltyp		Zytolyse		diff. atyp. Zellen	
Datum				Mischflora		undiff. atyp. Zellen	
				Trichomonaden		Endocervikale Zellen	
	Gruppe :			Fungi		Ektocervikale Zellen	
Photo-Nr.				keine bakt. Flora		Endometriumzellen	
		Histiozyten					
		Leukozyten					
		Erythrozyten					

EKAHA 822478. EKAHA-Organisation — Edler & Krische, Hannover. 7 1

Präparat-Nr.	Grad :	Mischtyp		Kokkentyp		Dyskarios. O'Zellen	
		Mucosustyp		Doederlein		Dyskarios. tief. Zellen	
		Mangeltyp		Zytolyse		diff. atyp. Zellen	
Datum				Mischflora		undiff. atyp. Zellen	
				Trichomonaden		Endocervikale Zellen	
	Gruppe :			Fungi		Ektocervikale Zellen	
Photo-Nr.				keine bakt. Flora		Endometriumzellen	
		Histiozyten					
		Leukozyten					
		Erythrozyten					

Präparat-Nr.	Grad :	Mischtyp		Kokkentyp		Dyskarios. O'Zellen	
		Mucosustyp		Doederlein		Dyskarios. tief. Zellen	
		Mangeltyp		Zytolyse		diff. atyp. Zellen	
Datum				Mischflora		undiff. atyp. Zellen	
				Trichomonaden		Endocervikale Zellen	
	Gruppe :			Fungi		Ektocervikale Zellen	
Photo-Nr.				keine bakt. Flora		Endometriumzellen	
		Histiozyten					
		Leukozyten					
		Erythrozyten					

Präparat-Nr.	Grad :	Mischtyp		Kokkentyp		Dyskarios. O'Zellen	
		Mucosustyp		Doederlein		Dyskarios. tief. Zellen	
		Mangeltyp		Zytolyse		diff. atyp. Zellen	
Datum				Mischflora		undiff. atyp. Zellen	
				Trichomonaden		Endocervikale Zellen	
	Gruppe :			Fungi		Ektocervikale Zellen	
Photo-Nr.				keine bakt. Flora		Endometriumzellen	
		Histiozyten					
		Leukozyten					
		Erythrozyten					

Präparat-Nr.	Grad :	Mischtyp		Kokkentyp		Dyskarios. O'Zellen	
		Mucosustyp		Doederlein		Dyskarios. tief. Zellen	
		Mangeltyp		Zytolyse		diff. atyp. Zellen	
Datum				Mischflora		undiff. atyp. Zellen	
				Trichomonaden		Endocervikale Zellen	
	Gruppe :			Fungi		Ektocervikale Zellen	
Photo-Nr.				keine bakt. Flora		Endometriumzellen	
		Histiozyten					
		Leukozyten					
		Erythrozyten					

Histologie		
Datum		

Bem.:

CANCER SOCIETY OF THE STATE OF NORDRHEIN-WESTFALEN, GERMANY
Dir.: Prof. Dr. H.K. Zinser

Name		First Name	Indicate previous No. if repeat smear
Age	Date of Birth	Address (not important)	

Present menstrual history:				Previous therapy:	
Pre-menarche				Surgery:	
Primary amenorrhea				Removal of cervix	
Regular cycle (L. M. P.)				Hysterectomy	
Irregular cycle				Subtotal hysterectomy	
Secondary amenorrhea				Unilat. oophorectomy	
Menopause				Bilat. oophorectomy	
Para	Now pregnant	Yes		Radium/X-ray therapy:	
		No		Cancer - dosage	
Abortion				Radium - menopause	
		Month		X-ray - menopause	

Clinical diagnosis:
(incl. speculum findings)

Colposcopy		No. of photo
Date		No. of photo

No. of specimens	Grade:	Mixed		Cocci		S. C. dyskaryosis	
		Mucous		Doederlein		Deep C. dyskaryosis	
		Deficiency		Cytolysis		Diff. atyp. cells.	
				Mixed		Undiff. atyp. cells	
Date	Group:			Trichomonads		Endocervical cells	
				Fungi		Ectocervical cells	
No. of photo		Histiocytes		No bact. flora		Endometrial cells	
		Leukocytes					
		Erythrocytes					
No. of specimens	Grade:	Mixed		Cocci		S. C. dyskaryosis	
		Mucous		Doederlein		Deep C. dyskaryosis	
		Deficiency		Cytolysis		Diff. atyp. cells	
				Mixed		Undiff. atyp. cells	
Date	Group:			Trichomonads		Endocervical cells	
				Fungi		Ectocervical cells	
No. of photo		Histiocytes		No bact. flora		Endometrial cells	
		Leukocytes					
		Erythrocytes					
No. of specimens	Grade:	Mixed		Cocci		S. C. dyskaryosis	
		Mucous		Doederlein		Deep C. dyskaryosis	
		Deficiency		Cytolysis		Diff. atyp. cells	
				Mixed		Undiff. atyp. cells	
Date	Group:			Trichomonads		Endocervical cells	
				Fungi		Ectocervical cells	
No. of photo		Histiocytes		No bact. flora		Endometrial cells	
		Leukocytes					
		Erythrocytes					

Histology	
Date	

Remarks

ABSTRACTS

This portion of ACTA CYTOLOGICA includes abstracts (approximately 150–300 word each) of papers, either recently published or accepted for publication. Authors are invited to submit their own abstracts. Authors are requested to forward to the Editorial Office a complete manuscript or reprint of the original paper together with their abstract. All figures should be included.

The Editorial Office maintains a *free Literature Service* for distribution of available papers to cytologists. Authors are requested to send a minimum of 10 reprints, if possible, 150 copies of published papers to the Editorial Office. The Literature Service will make photostatic reproductions of papers which are unobtainable whenever possible.

RÉSUMÉS

Cette rubrique des ACTA CYTOLOGICA contient des résumés (d'environ 150 à 300 mots) de publications qui ont été récemment publiées ou acceptées pour la publication. Les auteurs sont priés de présenter leurs résumés *en anglais*. Les auteurs sont invités à faire parvenir au bureau de rédaction, en même temps que leur résumé, un manuscrit complet comprenant toutes les illustrations ou un tiré-à-part du travail original.

Le bureau de rédaction entretient *un service gratuit d'information littéraire* pour la distribution aux cytologistes de toute publication disponible. Les auteurs sont priés d'adresser au bureau de rédaction un minimum de 10, si possible 150 copies ou tirés-à-part de travaux publiés. Le service de documentation fera dans la mesure du possible des photocopies des publications épuisées.

ZUSAMMENFASSENDE BERICHTE AUS DER ZYTOLOGISCHEN LITERATUR

Dieser Teil der ACTA CYTOLOGICA beinhaltet zusammenfassende Berichte (von etwa 150 bis 300 Worten) von wissenschaftlichen Veröffentlichungen, die entweder schon publiziert oder zur Publikation angenommen worden sind. Autoren sind hiermit eingeladen, Zusammenfassungen ihrer Arbeiten (*in englischer Sprache*) an die Schriftleitung zu senden. Die Autoren sind gebeten, der Schriftleitung das vollständige Manuskript mit allen Abbildungen oder den Sonderdruck der Arbeit einzureichen.

Die Schriftleitung unterhält einen *kostenlosen Literatur-Dienst* zur Verteilung von wissenschaftlichen Arbeiten. Autoren sind gebeten, der Schriftleitung mindestens 10, möglichst aber 150 Kopien von Sonderdrucken ihrer Arbeiten einzureichen. Der Literatur-Dienst steht auch nach Möglichkeit zur Herstellung von Lichtkopien von schwer zugänglichen Arbeiten zur Verfügung.

RESUMENES

Esta parte de ACTA CYTOLOGICA incluye resúmenes (aproximadamente de 150–300 palabras cada uno) de los trabajos, publicados recientemente, o aceptados para su publicación. Los autores deberán enviar sus resumenes *en inglés*. Se requiere a los autores para que envien a la Oficina Editorial, junto con su resumen, un manuscrito completo o separata del trabajo original. Deberán incluirse todas las figuras.

La Oficina Editorial mantiene *un Servicio de Literatura, gratuito*, para la distribución de trabajos disponibles. Se ruega a los autores que envien a la Oficina Editorial un minimo de 10 copias de sus trabajos publicados y, de ser posible, 150 copias. El Servicio de Literatura hará, siempre que ello sea posible, reproducciones fotostáticas de los trabajos que los autores no puedan obtener.

CANCER CYTOLOGY

PARATYPICAL LESIONS OF THE EPITHELIUM OF THE PORTIO VAGINALIS UTERUI AS THE PRE-CANCEROUS STATES

ANTONI BIELECKI - Ginekologia Polska 5:57, 1957.

The author discusses "paratypical lesions" of the stratified squamous epithelium of the portio vaginalis uteri. A strict evaluation on the basis of a morphological test is sometimes extremely difficult due to unspecific lesions especially in erosions.

The author applied in his investigations the histochemical method in evaluation of "paratypical lesions" of the stratified squamous epithelium of the Portio vaginalis uteri. The desoxyribonucleic acid content in the nuclei of cells of tissue samples has been determined quantitatively in 20 cases of "paratypia" of various intensities: "paratypia" of slight degree - 6, of moderate degree - 5, and of a marked degree - 9 cases.

The author suggests that larger or smaller content of desoxyribonuclieic acid may mean intensification or decrease of the dynamics of cellular hyperplasia. If this is so, then this hyperplastic activity in the "paratypia" cases is - as has been shown by the author's observations - distinctly decreased as compared with the hyperplastic intensity in the preinvasive and invasive cancer. The level of the desoxyribonucleic acid content in the examined preparations corresponded in a considerable degree to the intensification of a "paratypical" process.

The application of the described histochemcial method (Feulgen) may be a criterion in the evaluation of the "paratypical process" both as concerns prognosis and the therapeutical management and as an auxiliary test in the final morphological diagnosis. (Author's Abstract)

A POSITIVE CYTOLOGY REGISTRY: SOME OBSERVATIONS ON THE EFFECT OF PREGNANCY MADE WITH ITS ASSISTANCE

J. H. FERGUSON and D. CAVANAGH – Am. J. Obst. & Gyn. 76:773-782, 1958.

This is a progress report of observations that are being made on genital cancer with the assistance of a Positive Cytology Registry. For matriculation in the Registry a patient must have a Papanicolaou Class III, IV or V smear. At the time of this report there were 443 women in the Registry and they were the yield from 19,000 examinations. The need to include all women regardless of age in cytologic surveys is supported by our figure of 31 per cent of our patients being 29 years of age or younger. A significantly small percentage of our patients were found to be nulligravidas. The ability of our diagnostic work, particularly the cone biopsy, to eradicate normal tissue was demonstrated. The indications for conization in pregnancy have been the same as in the non-pregnant women. There is a possibility that the conization operation during pregnancy is the cause of an increase in premature labors. Adjunctive services of the Registry lie in health education of the patient, maintenance of all cytology records, and the acquisition of as complete a history of exfoliative cytology as possible in each patient. The expansion of our cytology service to include the obtaining of smears on women admitted in labor to the delivery unit was described. One hundred and eighteen women who lost their positive cytology without the benefit of radiotherapy or hysterectomy were analyzed and the effect of our diagnostic studies on the cervix were noted. (Authors' abstract)

PATTERNS OF EARLY INVASION FROM INTRA-EPITHELIAL CARCINOMA OF THE CERVIX

H. K. FIDLER and D. A. BOYES - Cancer (Date of acceptance for publication: August, 1958).

During the investigation of 419 cases of intra-epithelial carcinoma of the cervix, 26 cases (6%) were discovered to have microscopic foci of invasion.

It is our opinion that intra-epithelial carcinoma with discrete micro-invasive foci ("Stage 0+") warrants a special category, if only for study purposes. The diagnostic criteria are often not well defined, and the general tendency is to over-diagnose and place too many cases in this group. What we consider to be simulated invasion and true invasion have been illustrated with photomicrographs. The evaluation of this type of case can be carried out with accuracy only by the use of cone biopsy, serially blocked and step serially sectioned. The prognosis in this stage probably closely approaches that of Stage 0, if total hysterectomy is performed. It should be noted, however, that three of our cases had lymphatic permeation and these, we believe, should be treated as Stage I carcinoma. In none of the 26 cases has recurrence or metastases been noted. The follow-up period, however, is too short in most of our cases to be dogmatic regarding results.

This lesion should be distinguished from occult carcinoma in which there are confluent, frankly invasive foci, since in the fourteen cases of occult carcinoma that we have studied, three patients have died of their disease.

In over half the cases having discrete invasive foci there were maturing and, occasionally, degenerating changes of the cells. These phenomena are morphologically similar to the changes seen in carcinoma of the cervix that is responding well to irradiation, and they also resemble the appearance occasionally seen in spontaneously regressing, metastatic squamous carcinoma in lymph nodes. These features suggest to us a pattern of genesis which may apply over the relatively long period of time in which a predominantly intra-epithelial lesion is developing the characteristic of frank invasion. A purely non-invasive carcinoma is in itself harmless. Early invasion is not necessarily harmful or synonymous with metastasis. That many people live in harmony indefinitely with neoplastic lesions seems likely, and we suspect that this situation is represented by those maturing and degenerating foci shown in this and other papers. What upsets this balanced relationship between tumor and host, with resulting unrestrained spread of the neoplasm, is not known, but the cause of this upset may be as important as the initiating carcinogenic factor. (Authors' abstract)

EXPERIENCE WITH VAGINAL AND CERVICAL SMEAR TECHNIQUES AS AN OFFICE PROCEDURE

A. M. GOODWIN – Am. J. Obst. & Gyn. 75:970-975, 1958

Routine smears were taken from 734 unselected patients in a gynecologist's office. Pregnant patients were included.

Smears were taken by pipette, eustachian canula or cotton swab from the endocervix, and from the squamo-columnar junction by wooden spatula. An even spread was made by placing one slide upon the other and then drawing them apart.

A modification of Papanicolaou's stain was found superior to silver carbonate or hematoxylin and eosin. Technicon dehydrant replaced costly alcohols and was found satisfactory.

Positive smears were obtained in nine cases. By deep, sharp knife, cone biopsy seven were confirmed to be carcinoma of the cervix, all unsuspected. Six were in situ carcinomas and one was invasive. One patient was pregnant. Two smears were proven to be endometrial cancer.

Two illustrative cases are presented with photomicrographs.

Conclusions:

1. No gynecological examination by a specialist is complete without cytological study.
2. Every gynecologist should be familiar with a reliable technique for preparing smears.
3. Pregnant women should be included.
4. No cervix should be treated by cautery or hysterectomy or amputation of the cervix performed without prior cytological study.
5. The profession should encourage the training of cytologists and the establishment of laboratories for cytological screening.

Addendum:

At time of writing, 2130 patients have had smears taken and 11 additional cases of cancer in situ have been discovered, only one suspected. Annual repeat smears from 472 women revealed no positives. (Author's abstract)

CONTRIBUTION TO THE STUDY OF INTRACELLULAR POTASSIUM. THE CORRELATION BETWEEN POTASSIUM AND THE TENDENCY OF NEOPLASTIC PROLIFERATION.

C. HEROVICI and V. ACOSTA – Bulletin du Cancer 45:38-45, 1958

In using Marza's modification of MacCallum's technique, the authors have been able to show the presence of proteidic potassium in the region of the cells taken from the cervico-vaginal swabs.

One hundred ten samples have been examined by this technique, among which 18 were from normal cervices, 22 infected cervices, 5 atrophic cervices, 36 with benign proliferations of the cervix, (ectropion, polyp, hyperplasia of the mucous membrane of the endometrium), 24 epitheliomas and 5 cervical epitheliomas which had been treated by radium therapy.

The results of this research seem to indicate that the quantity of intracellular potassium is proportional to the size of the tumor and also to its tendency to proliferate, but on the other hand, it seems to have no relationship to malignancy. It is, on the whole, a test for the rapidity of growth of a lesion. (Authors' abstract)

LOCALIZATION OF THE MAIN COLPOSCOPICAL FINDINGS WITH INCREASED ATYPICAL EPITHELIUM AND MICROCARCINOMA
(LOKALISATION DER KOLPOSCOPISCHEN HAUPTBEFUNDE BEI GESTEIGERT ATYPISCHEM EPITHEL UND MIKROCARCINOM)

R. HOHLBEIN, – Zbl. Gynäk. 80:738, 1958

In a survey of 327 cases of increased atypical epithelium and 88 cases of microcarcinoma, we found that the main localization of the lesions is not at the anterior pole of the anterior lip (12 o'clock) or the posterior pole of the posterior lip (6 o'clock). The lesions are distributed evenly over the surface of the entire cervix. However, the anterior lip is slightly favored as the site of such lesions. Therefore, it is not proper technique to routinely do a biopsy always from the same site, e.g., 12 o'clock or 6 o'clock, in the hope of finding some of the atypical epithelium.

Thus it is absolutely necessary, before every biopsy (or other diagnostic procedures), to have a careful colposcopical examination of the cervix uteri. (Author's abstract)

THE SIGNIFICANCE OF CYTOCHEMICAL CRITERIA FOR PROGNOSIS IN A SERIES OF 117 CASES OF CARCINOMA OF THE CERVIX

C. HEROVICI and CAO XUAN AN – Bulletin du Cancer 45:83-91, 1958

This work is a follow-up of a paper given to the Association Francaise pour l'Etude du Cancer (1955), in which the authors gave a method for cytological evaluation of radio-sensitivity, based on the modifications of the nucleic acids under the influence of ionizing radiations. The presence of these nucleic acids is shown by means of a variation of Brachet's mixture; this variation consists of the addition of orange C to methyl-pyronine green, which gives a quantitative stain for RNA.

One hundred and seventeen cases of cancer of the cervix have been examined by the cytochemical technique before and after treatment; in favorable cases the prognosis, based on the decrease of DNA. and the increase of RNA., has been confirmed for 80% of the cases two years after treatment.

The authors intend to improve on this percentage by using this test for histodiagnosis, in conjunction with Gluckman's test for cellular differentiation, and also with the various criteria of histoprognosis supplied by the conjunctive tissues. (Authors' abstract)

SITE OF MARKED EPITHELIAL ATYPIA AND MICROCARCINOMA IN THE ENDOCERVIX (DIE INTRAZERVIKALE LOKALISATION DES GESTEIGERT ATYPISCHEN EPITHELS UND DES MIKROKARZINOMS)

R. HOHLBEIN and R. KRIMMENAU – Geburtsh. u. Frauenhlkde 18:1030, 1958

One hundred twenty-three cases of carcinoma in situ and 14 cases of established carcinoma (microcarcinoma) of the portio vaginalis and the cervical canal are reviewed. The site of the process was located by serial sections, and the following observations were made: carcinoma in situ was situated at the portio vaginalis in 30.1%, at the portio vaginalis and the lower portion of the cervical canal in 64.2%, predominantly in the cervical canal in 1.6%, and entirely in the cervical canal in 4.1% of the cases. Of the 14 cases of microcarcinoma 5 were confined to the portio vaginalis. In 6 cases the portio vaginalis and the lower portion of the cervical canal were involved. In 2 cases the location of the carcinoma was predominantly, and in one case exclusively, in the cervical canal. The latter was, therefore, the main seat of the degenerative changes in 5.7% of the patients with carcinoma in situ, and in 14.3% of the patients with microcarcinoma.

A number of case histories are reviewed.

The role of cytology in the diagnosis of intracervical carcinomatous processes is discussed. (Authors' abstract)

THE RADIATION REACTION IN THE VAGINAL SMEAR AND ITS PROGNOSTIC SIGNIFICANCE

O. KJELLGREN – Acta Radiologica, Supplementum 168:1-170, 1958

The literature on gynecological exfoliative cytology, especially radiation cytology, is surveyed.

Two hundred and eighty-seven patients with cervical cancer treated according to the Stockholm method were studied. Factors thought capable of influencing the radiation reaction in the vaginal smear were analyzed, and the prognostic significance of the radiation reaction was studied. The patients were classified as having a good or a poor response with the dividing line being 60% of the benign exfoliated cells changed by radiation.

There was no evidence that the response was influenced by International Stage, duration of history, number of pregnancies, gross tumor type or radium dose within therapeutic limits. It was found that the radiation reaction is correlated with menopausal state, with hormonal activity in the pretreatment smear and with the age of the patient.

Analysis of the prognostic significance of the radiation reaction showed that the five year recovery rate, the primary local healing rate, and the local five year healing rate were significantly higher in the good response group. The local recurrence rate was significantly higher in the poor response group. No difference was found in the metastasis rate between the poor and good response groups with local healing. Radiation injuries were about three times more frequent in the good than in the poor response group. (Author's abstract)

INDUCED CERVICAL CARCINOMA OF THE MOUSE. A QUANTITATIVE CYTOLOGIC METHOD FOR EVALUATION OF THE NEOPLASTIC PROCESS.

I. KOPROWSKA, J. BOGACZ, C. PENTIKAS and W. STYPULKOWSKI - Cancer Research 18:1186-1190, 1958

Invasive cervical and/or vaginal carcinoma was induced in 100 per cent of C3H mice within a period of 4-1/2 - 5 months by applying 3-4 benzpyrene to the cervix through an otic speculum. The development of carcinoma may be evaluated accurately by a team of co-workers without taking measurements and without labeling individual exfoliated cells. By scoring cytologic criteria of malignancy in weekly vaginal smears, cytologic patterns are obtained which permit diagnosis of the presence of carcinoma and distinguish between early and advanced stages of malignant disease, but do not determine presence or absence of invasion. Smears from mice with early carcinoma were characterized by the persistent presence of at least five of the factors of abnormality, including usually more than one nuclear abnormality. As the neoplastic process extended, both the quantitative and qualitative scoring became higher. In terminal stages there was decreased exfoliation accompanied by marked infection and necrosis. This cytologic method of evaluation of a neoplastic process may also be used for determining the effect of substances being tested for interference with carcinogenesis. (Authors' abstract)

A SOURCE OF FALSE POSITIVES IN CYTOLOGIC INTERPRETATION

M. MILLIGAN, L. A. CARROW and V. EGGERS - Am. J. Obst. & Gyn. (Date of Acceptance for publication: October, 1958)

A small round or oval-shaped structure with a strong affinity for Harris hematoxylin has, in the past, been responsible for some false positive cytologic diagnoses. These structures have been designated as "blue blobs" by the authors. In the past, they have been interpreted as malignant free nuclei; they are now disregarded. They were seen in the cytologic smears of 53 patients; 94.3% of these patients were postmenopausal.

In the smears from these 53 patients, trichomonads were recognized in 46 or 86.8% of the total. In addition, six patients who did not exhibit trichomonads cytologically had cellular debris which was consistent with the presence of trichomonads.

These "blue blobs" were responsible in four cases for a cytologic diagnosis of carcinoma and in another four of moderately atypical squamous cells. Tissue obtained failed to substantiate these diagnoses. There have been no "blue blobs" co-existing with carcinoma of the cervix or body of the uterus. Estrogen stimulation appears to decrease the number of "blue blobs" or eliminates them entirely.

The authors feel that there is some relation between these structures and the trichomonad in the absence of estrogen. However, they have not yet been able to demonstrate definitely whether or not these "blue blobs" are trichomonads. (Authors' abstract)

FIRST RESULTS OBTAINED IN THE CONSULTATION OF THE PROPHYLAXIS OF UTERINE CANCER

F. NOGALES, E. VILAR and L. MONTALVO - Gynecological Act. 9:459, 1958

Although for many years we have been studying uterine cancer by the separate methods of colposcopy, histology and cytology, the joining together of these explorations could not have been done before because of material difficulties to get the required apparatus. However, today we can say that we have the first organized and systematized consultation in the struggle against uterine cancer, thanks to the direction of Professor Botella Llusia.

Of the 1185 patients visiting the general consultation, 189 of them were sent to us for colposcopic and complementary exploration. No patient had metrorrhagia. Ages ranged between 20 and 70 years.

Age:	20 - 29	30 - 39	40 - 49	50 - 59	over 60
Number of cases:	27	87	56	15	4
Carcinoma:	1	4	2	0	1

Cytology was applied to 155 patients, resulting in 10 POSITIVE cases, (Grade IV, Papanicolaou), and biopsy was done on 7, which completely agreed with the cytology. Biopsy was not done on the other 3 as they did not come back for consultation.

We performed biopsies on 66 patients of this series and besides agreeing with the cytology, a comparative study with colposcopy shows the following result:

Agreement of both explorations . . . . . .50 cases

Both images offering certain similarities . . . . . 8 cases

Complete lack of coincidence . . . . . 8 cases

Most of this lack of coincidence is due to the biopsy, which did not touch the right spot.

We believe with Professor Botella that the combining of these three explorations is the ideal technique for discovering cervical cancer.

THE STAINING WITH METHYL-GREEN PYRONINE AND THE FEULGEN REACTION APPLIED IN A CYTOCHEMICAL STUDY OF NEOPLASIA OF THE FEMALE REPRODUCTIVE TRACT (LA COLORAZIONE CON VERDE DI METILE-PIRONINA E LA REAZIONE DI FEULGEN APPLICATE ALLO STUDIO CITOISTOCHIMICO DELLE NEOPLASIE CENITALI FEMMINILI)

G. SANI – Rivista Italiana di Ginecologia 41:113-163, 1958

A cytochemical study of the behavior of the nucleic acids in vaginal and uterine cancers was performed. The smears and the control sections were colored with both the Feulgen reaction and methyl-green pyronine mixtures dissolved in buffer solutions at a different pH, according to the Gerola and Vannini method; some were previously treated with ribonuclease, according to Brachet.

The basic dyes showed some advantages, compared with the other routine methods, in demonstrating the tumor elements.

Observing the findings obtained, the author thinks that the tumor cells may be divided into two main groups. These two types of cells, with their intermediate and transitional forms and with completely different metabolic characteristics of the nucleic acids, represent the proliferative and dedifferentiating regressive phase of the tumor, respectively.

The morphological and cytochemical features of such elements, which are found in the smears and the sections, are described in detail.

Particular attention was paid to the nucleolar apparatus, which is almost always present in the tumor cells. According to the hypothesis suggested by Caspersson, the possibility was discussed that the nucleoli with the "nucleolus-associated chromatin" might represent the "primum movens" of the cytoplasmic protein syntheses. In this connection, the author tries to explain the changeable distribution of the nucleic acids observed in the endometrial tumor cells, and particularly the cytoplasmic RNA.

On the basis of the results obtained, the author believes that the method employed in this research may not only have advantages in the study of the tumor cells, but also may be used for diagnostic and prognostic purposes. (Author's abstract)

SIGNIFICANCE OF PERFORMING DUAL SMEAR EXAMINATION IN A MASS SCREENING SURVEY FOR UTERINE CANCER

Y. S. SONG, H. FANGER and T. H. MURPHY – Am. J. Obst. and Gyn. (Date of Acceptance for Publication: December 1958)

Twenty-five thousand cases were screened by dual smear examinations in a project for the detection of uterine cancer in asymptomatic females. A comparison study was made of the accuracy of vaginal aspiration and cervical scraping smears in carcinoma in situ, invasive carcinoma of the cervix, and adenocarcinoma of the fundus. In 148 cases of carcinoma in situ (confirmed by cone biopsy, using step serial section) 45 cases were detected by cervical scraping smears, 9 by vaginal aspiration smears and 94 by evidence on both smears. In 28 cases of squamous carcinoma of the cervix, 6 were detected by cervical scraping smears, 3 by vaginal aspiration smears and 19 by evidence on both smears. In 19 cases of adenocarcinoma of the fundus, 4 were detected by cervical scraping smears, 5 by vaginal aspiration smears and 10 by evidence on both smears.

After diagnosis of carcinoma in situ on the basis of cone biopsy specimens from 92 cases, examination of 55 subsequent hysterectomy specimens revealed residual carcinoma in situ in 11 cases, suggesting that cervical cone biopsy as a therapeutic method might not have been satisfactory.

Continued examination of both types of smears seems justified in a subsidized mass screening survey for uterine cancer, since both specimens offer a definite diagnostic value. (Authors' abstract)

A METHOD OF TAMPON SWABS FOR CYTOLOGICAL DIAGNOSIS OF CANCER OF THE UTERUS (ÜBER EINE TAMPONAUSSTRICHMETHODE IN DER ZYTOLOGISCHEN DIAGNOSTIK)

K. TIETZE — Geburtshilfe and Frauenheilkunde 18:746, 1958

General practitioners do not concern themselves sufficiently with the cytological recognition of the early stages of cancer of the uterus, since the swab method and the dispatch of specimens to laboratories take too much time and trouble. Therefore, the author has developed a process to help the general practitioner in his work. In any particular case the laboratory sends a tampon containing Thyrofusin-K-Solution and a salt and sugar mixture. The tampon is placed in the vagina close to the cervix uteri, left in place for 12 to 24 hours, removed by the patient herself and dispatched by mail to the laboratory in the container provided. On arrival of the pad, it is soaked in normal saline and smears are made from the wet tampon on the microscopic slide and then stained by the Papanicolaou method. The author has tested the method with a group of general practitioners and specialists. Out of 211 tampon swabs, 23 were held for further examination; out of these, three early cancers were diagnosed by cytological methods alone (two surface carcinomas, one microcarcinoma). Furthermore, nine additional cases of carcinoma colli uteri were discovered, but the specialist had already been able to recognize them as cancer microscopically. Three cases were false positive, two cases false negative and seven suspicious.

Initial experiences encourage further application of the tampon swab method described. (Author's abstract)

THE IMPORTANCE OF THE SITE FROM WHICH CYTOLOGICAL SMEARS ARE TAKEN (DIE BEDEUTUNG DES ORTES DER ENTNAHME FÜR DIE ZYTOLOGISCHE KREBSFÄHRTENSUCHE)

H.-J. SOOST – Der Krebsarzt 9:408-420, 1958

In 25 women with carcinoma of the cervix, 104 cytological smears were taken from various sites. After counting over 30,000 cells and comparing their sites of origin, it appears that the prospects of finding cells which are both suspicious of carcinoma and in good condition are best in smears taken from the cervical portio. In doubtful cases a smear taken with an Ayre spatula will make the diagnosis more certain. Smears taken from the cervical canal often contain autolytic cell debris, which makes the examination more difficult. Among 30 smears taken from the posterior fornix, 4 contained no suspicious cells whatever and 5 gave rise to doubtful findings only. If the first examination of a cytological specimen does not give a definite result, further examinations are recommended of smears taken simultaneously from the portio, from the cervical canal and from the posterior fornix. (Author's abstract)

EXAMINATIONS OF CARCINOMA OF THE CERVIX UTERI BY MEANS OF PHASE CONTRAST MICROSCOPY (UNTERSUCHUNGEN DER PORTIO-KARZINOME MIT HILFE DER PHASENKONTRAST-MIKROSKOPIE)

J. ŠVEDJDA, M. HRDLIČKA and B. PTÁČKOVÁ – Z. Geb. und Gynäk. 15:193, 1958

Phase contrast microscopy is a quick and simple method for the diagnosis of carcinoma of the cervix uteri. Its simplicity makes it a suitable method for mass examinations of women. This method has been used by the authors since 1953: A total of 357 women have been examined with this method. Since 1953, 236 of them showed symptoms, clinically and colposcopically, of carcinoma. Out of this group, 226 cases (95.7%) were diagnosed by the described method. In 86% of the cases of this group, the type of lesion also could be determined. Only in 10 cases (4.3%) was a false negative cytological diagnosis given. In spite of these good results, phase contrast microscopy is an auxiliary method which has its value only in connection with other diagnostic methods. Its great advantage is the possibility of examining living cells, and for this reason we use it to observe cellular changes during radiation therapy. From this point of view it is a promising method to use in connection with cytochemical and histochemical procedures. (Authors' abstract)

HORMONAL CYTOLOGY

THE EFFECTS OF ESTRIOL ON THE UTERUS, CERVIX AND VAGINA (STUDIES WITH LARGE (30 mg) AND MINIMAL (50 γ) DOSAGES)

A. PUCK, W. KORTE and K.-A. HÜBER – Deutsche Medizinische Wochenschrift 44:1864-1866, 1957

Estriol has been considered a metabolic breakdown product of estradiol and not a follicular hormone, because the effecting of endometrial proliferation and the characteristic changes in the vagina require an

estriol dose 300 times that of estradiol. However, intra-muscular injection of a total of 30 mg (or 50 γ) of estriol in 5 equal parts to 9 women at least 5 years in menopause produced specific effects on the genitalia. Biopsy specimens taken before treatment and three to five days afterwards showed the following changes in the uterus, cervix and vagina: (1) Atrophic vaginal epithelium regained its normal layering; cervical glands increased in number and began to secrete again; there was proliferation of the basal layer of the uterine epithelium; the glands showed degenerative changes resembling those seen in glandularcystic hyperplasia. (2) There was stimulation of the fixed connective tissue elements and interstitial increase of water, almost to the point of edema formation. Even the minimal doses of estriol produced the cervical and vaginal changes. Estriol is thus indicated, if one wishes to produce only cervical and vaginal epithelial proliferation without influencing the endometrium. (Authors' abstract)

CYTOLOGY IN INFLAMMATORY REACTIONS

THE DETECTION OF TRICHOMONAS BY METHODS OF IMMUNIZATION

WOLFGANG KORTE - Comptes Rendus de la Societe Francaise de Gynecologie :1 pp. 159-162, 1958

In the lecture on diseases caused by trichomonads held at the International Symposium in Reims, France, in May, 1957, the conception of pathogenicity of micro-organisms for the human body is discussed. An infection does not prove a pathogenic effect. Inflammation is only one possible way of an organism reacting to an infection. Other forms of reaction such as disturbances of metabolism and circulation, alterative and degenerative processes, hyperplasia and immune-biological products of cells or tissues can likewise be used for the demonstration of pathogenic qualities of micro-organisms.

It was demonstrated on 256 women infected with Trichomonas that the human organism is able to form specific antibodies against trichomonads. The examinations were implemented by means of the complement fixation from venous blood. The nature of the incidence of trichomonads was examined clinically and cytologically.

Characteristic differences in the height of titer can be noticed before and after treatment. In chronic incidence of trichomonads, the height of titer is no definite indicator for the severity of a local change. It is necessary to notice the beginning and the temporal course of a disease caused by trichomonads with the aid of various immune-biological tests. It is probable that the "KBR" (complement fixation reaction) may be negative, while other test methods still show the existence of the infection and the reaction of the organism by positive results. (Author's abstract)

EXAMINATIONS OF TRICHOMONAS VAGINALIS

WOLFGANG KORTE - Archiv für Gynäkologie, Band 189 (31. Verhandlungsbericht der Deutschen Gesellschaft fur Gynäkologie Heidelberg 1956

The species "Trichomonas vaginalis" was found by examination of the length of the cell body, number of flagella and behavior of the undulating membrane in 50 strains of trichomonads, which had been cultivated in pure culture under equal conditions. One thousand cytometrically examined flagellates (20 at a time per strain) showed an average length of 15μ with a range of from 9 to 30μ. Exact morphological examinations are necessary to delimit the Trichomonas species which are found in the human being.

Fifteen different methods of demonstrating trichomonads by staining were tested. A new possibility is to electively demonstrate trichomonads with acridine-orange and fluorescence microscopy. The conception of the so-called erosive trichomonad-colpitis, demonstrable in the cytological smear preparation, is explained. Combined clinical, cytological and serological examinations of Trichomonas vaginalis show that the organism forms specific antibodies against Trichomonas vaginalis. (Author's abstract)

CYTOLOGICAL TECHNIQUES

VAGINAL, CERVICAL AND ENDOCERVICAL CYTOLOGIC SMEARS ON A SINGLE SLIDE

G. L. WIED and G. F. BAHR – Obstetrics and Gynecology (Date of Acceptance for Publication: February 17, 1959)

The preparation of the three required cytological smears (vaginal, cervical and endocervical specimens) on one glass slide is discussed as to its advantages and disadvantages for routine screening purposes. The diagnostic accuracy of exfoliative cytology on three smears on one slide is higher than the diagnostic accuracy on cervical smears only, as far as cervical cancer screening is concerned. An experimental test using chicken and sheep erythrocytes showed that the diagnostic accuracy of smears on regular glass slides and the so-called "V-C-E" slides is fully comparable. In comparing the "V-C-E" slide with the individual glass slide, it was found that the diagnostic accuracy did not decrease with the "V-C-E" slide, although there is less glass area available on which to spread the specimens. Other advantages of preparation of the "three smears on one slide" are discussed. The "three smears on one slide" technique has been in use over a period of more than seven years and can be recommended for routine application. (Authors' abstract)

OTHER PHASES OF CYTOLOGY

NUCLEAR CHANGES IN ORAL EPITHELIAL CELLS IN SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD DUE TO VITAMIN-B12 DEFICIENCY

S. T. BOEN, J. A. MOLHUYSEN, J. STEENBERGEN - The Lancet, 2:294-296, 1958

One of us described nuclear changes in oral epithelial cells in patients with pernicious anemia (Boen, 1957) (1). In association with marked nuclear polymorphism, the presence of giant nuclei was characteristic. These large nuclei were more or less round and had a finely reticulate chromatin structure. They were not found in other kinds of anemias.

In seven out of ten patients, nuclei with diameters of 14.5μ or more were found in an average of 26% (normal maximum 5%). Within one week after beginning treatment with vitamin B12, the nuclei became normal again.

Recently we described a woman, age 57, who had had subacute combined degeneration of the spinal cord for several months, but showed no changes in the blood or bone-marrow. She had a histamine-refractory achlorhydria. The diagnosis of vitamin B12 deficiency was made on the characteristic nuclear changes in the oral epithelium. On treatment with vitamin B12 she became much improved, and the nuclei of the oral epithelium became normal within a week from the start of treatment. No changes were seen in the hemoglobin concentration, reticulocyte counts, or serum-iron level. The diagnosis was confirmed by demonstration of a low serum-vitamin B12 level before treatment, (60 μ μg per ml.). (Authors' abstract)

SIMULTANEOUS CYTO-INTERPRETATION OF NATURE AND SEX OF TUMORS (GLEICHZEITIGE CYTO-INTERPRETATION VON NATUR UND GESCHLECHT DER TUMOREN)

W. E. COUTTS and E. SILVA-INZUNZA – Archiv für Geschwulstforschung 12:385-390, 1958

Phase contrast observation of fresh unfixed and unstained cells from surface scrapings of recently removed tumors allows one to establish simultaneously the nature and sex of tumors. Anisokaryosis, loss of the nuclear-cytoplasmic ratio, lobing or festooning of the nuclear membrane, and multiplicity of nucleoli are considered as signs of malignancy. Sex is evaluated on the basis of per cent of cells containing sex chromatin (Barr's corpuscle) in their nuclei. In order to classify tumors according to their chromosomal sex percentages, it is proposed that they be classified conventionally into different groups, since every human being is an intersex. Tumors in males containing from 0-10% SxChr are considered as male (♂), from 11-30% SxChr counts as viriloid intersexes (♂♀), from 31-50% as feminoid intersexes (♀♂) and from 51-80 or more as contrasexes (♀♀). Those from females containing from 80-51% SxChr counts are considered as female tumors (♀), from 50-31% as feminoid intersexes (♀♂), from 30-11% as viriloid intersexes (♂♀) and from 10-0% as contrasexes (♂♂). Advantages of this grouping are that one can prescribe, on a reasonable basis, homologous, heterologous or proportional combinations of sex hormones. One hundred and eighteen tumors from both sexes and different structures are analyzed. (Authors' abstract)

POSSIBILITIES AND LIMITATIONS OF COLPOSCOPY AND COLPOPHOTOGRAPHY AND THE COLPOPHOTOGRAPH WITH DIFFERENT MAGNIFICATIONS OF THE COLPOSCOPE

W. KORTE and W. KORTE and E. GERSING - Photographie und Wissenschaft and Zeiss-Mitteilungen 1:13-16, 1957; 132-137, 1958

Both works, extracts from a lecture to the Niederrheinische Gesellschaft fur Natur- und Heilkunde, Medizinische Abteilung zu Bonn, 1957, point to the practical possibilities of delimiting the changes of the external os of the uterus more exactly. Distinction is drawn between erosion, ectopia and ectropion, and resulting conditions, as well as atypical epithelial lining and carcinoma. Colored colpophotography is suitable for documents in the doctor's report.

The so-called "sector-photograph" enables one to register magnified parts of the cervix (and of the vagina and vulva too). The later enlargement of photographs is not adequate and should be replaced by photography of individual sectors (for example of the cervix), which are magnified by the resolving power of the colposcopic lens system. The apparatus is described. Pictures of the modified cylindrical specula, the apparatus and the original colored photos are shown. (Authors' abstract)

MAMMARY IMPRINTS, CYTOPATHOLOGICAL STUDY (L'EMPREINTE MAMAIRE, ETUDE CYTOPATHOLOGIQUE)

J. MOURIQUAND and M. DARGENT. – Bulletin du Cancer 44:449-465, 1957

Reviewing the data of 150 cases, the authors discuss the cytologic characteristics of mammary imprints concerning various benign and malignant diseases of the breast: intraductal papilloma, fibroadenosis, Schimmelbusch's disease and cancer.

The technique in use is extremely simple, allowing investigation of the whole tumor through numerous imprints. Staining and evaluation of the smears are quickly obtained when the cytologist is trained, giving to this method as much interest for the extemporaneous diagnosis of breast tumors as the frozen section one.

Lymph node imprints may be performed simultaneously to give information on lymph node involvement. (Authors' abstract)

ERRATUM*

ON PAGE 552 OF VOLUME II, NO. 3, 1958, A PART OF THE PAPER OF DR. LEOPOLD G. KOSS ENTITLED "CYTOLOGY OF CARCINOMA IN SITU OF THE ENDOMETRIUM" WAS INADVERTENTLY OMITTED. THE PAPER SHOULD READ AS FOLLOWS:

LEOPOLD G. KOSS

New York, New York, U.S.A.

While the concept of in-situ carcinoma of the endometrium may appear relatively new (1, 2), in reality the entity has been noted by Cullen (3) as far back as 1900 and was amply described by Meyer (4), who designated it by the simple name of "endometrial adenocarcinoma without evidence of invasion." I don't think that there has ever been a better definition of in-situ carcinoma than the one quoted above. In the case of the endometrium, the question of invasion is somewhat more easily settled than in the case of the cervix because of the anatomical setting and a sharp demarkation between the glandular endometrium and the myometrium. To my mind, the presence of CYTOLOGICALLY ABNORMAL endometrial glands NOT SURROUNDED BY ENDOMETRIAL STROMA within the uterine muscle constitutes evidence of invasion.

The question as to what constitutes endometrial carcinoma in-situ, as differentiated from abnormal or atypical or adenomatous hyperplasia (5) is not an easy one to answer. No matter how much has been written on this subject, this definition is primarily a matter of experience that can be, however inadequately, described but which cannot be taught. Carcinoma is a pattern of cells and tissues which has been recognized as capable of invasion and metastases. It is obvious that this experience varies from individual to individual and from institution to institution. No matter how astute the observer and how vast his experience, a certain number of patterns shall remain in doubt - as witnessed by the much quoted statement of Robert Meyer a propos an endometrial lesion: "kein Karzinom, aber besser heraus."

My personal experience agrees with that of TeLinde et al (6), and I believe that most of the endometrial lesions of dubious nature represent forms of early carcinoma.

The writer had the opportunity to observe cytologically and in tissue sections one dozen lesions that were diagnosed either as in-situ or very early invasive cancer of the endometrium. This limited experience does not allow any generalized statement pertaining to the cytologic findings. All of the patients falling into this category have been clinically post-menopausal, yet the make-up of the smears nearly invariably indicated an abnormally high degree of maturation of the squamous cells and presumably an abnormally high estrogenic activity. Contrary to advanced invasive cancer of the endometrium (7), the background of the smears was generally free of blood, either fresh or fibrinated, while some histiocytes were usually present. The cancer cells were as a rule very few, very inconspicuous and difficult to find. The individual cancer cells were usually not significantly larger than normal endometrial cells nor was their grouping of any particular diagnostic assistance. As is the rule in cancers in general, single cells were always available for inspection. The only truly significant cytologic finding in this group of patients, was the presence of moderate degrees of nuclear abnormality, especially multinucleation and the presence of abnormally large and occasionally multiple nucleoli. When the grouping allowed a comparison of individual cells, considerable degrees of anisonucleoisis could be observed. Nuclear hyperchromasia was not observed in the author's experience. The feature of infiltration of the cytoplasm of endometrial cancer cells by leukocytes, frequently so prominent in invasive endometrial cancer (7), was occasionally observed. In a case of adenocanthoma in-situ, abnormal squamous cells were observed as well. In summary, the cytologic findings were inconspicuous and difficult to recognize.

It is likely that the relative success which this laboratory has been enjoying within the last few years in detection of very early carcinoma of the endometrium is in a way due to a very poor performance in the years past. When, in the year 1954, it became obvious that the laboratory screeners and senior staff were missing approximately 50% of all endometrial cancers, a thorough review of the sources of error was undertaken. It became evident that casual screening of vaginal smears is a poor tool for detection of endometrial cancer.

Therefore, especially careful screening procedures were applied to the following categories of patients:

1. Postmenopausal patients with evidence of abnormally high maturation of squamous cells.
2. Patients shedding endometrial cells, however normal appearing, outside of the physiological menstrual bleeding.
3. All patients, age 45 or over, with either clinical or cytological evidence of abnormal bleeding.
4. All patients who have histiocytes in smears after the 12th day of the cycle.

Endometrial aspiration specimens have been of limited assistance. As a rule, when cancer is present it will be seen in the vaginal smear. This special care has rendered the results of screening for

* This erratum is Page 552A and 552B in Volume II, No. 3

endometrial cancer considerably more accurate, culminating in detection of several early cases of endometrial cancer.

Fig. 1. Vaginal smear containing two enlarged endometrial cells, one of which has at least two nuclei. The cytoplasm of this cell is densely infiltrated with polymorphonuclear neutrophiles. The three smaller cells on the right side of the picture display multiple nucleoli.

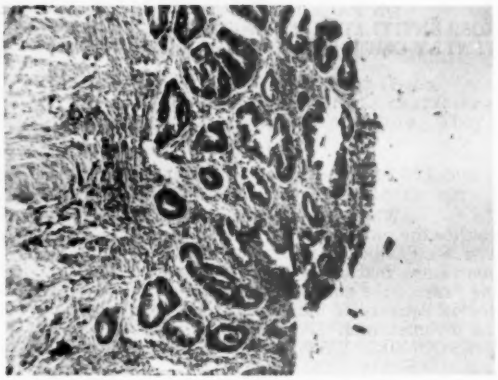


Fig. 2. The corresponding tissue section displays a highly abnormal endometrial pattern without any evidence of invasion.

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THIS AND THAT

This portion of ACTA CYTOLOGICA is devoted to miscellaneous information.

INFORMATIONS DIVERSES

Cette rubrique des ACTA CYTOLOGICA est destinée à des informations diverses.

PERSÖNLICHE INFORMATIONEN

Dieser Teil der ACTA CYTOLOGICA befasst sich mit verschiedenen persönlichen Nachrichten.

ESTO Y AQUELLO

Esta parte de ACTA CYTOLOGICA está dedicada a información diversa.

LUIGI BACIALLI OF BOLOGNA, ITALY, will attend meetings in Amsterdam, June 7 - 11 and Bari, Italy, September 27 - 30, 1959. He recently became Dean of the Medical School, University of Bologna, Italy. He published "Compendio di Ginecologia" and recently participated in Simposio sulla Sterilita in Milano, December, 1958.

LUDWIG von BERTALANFFY OF TOPEKA, KANSAS, U.S.A., presented "Application of the Acridine-orange Fluorescence Method to Lung Cancer" at the Second Workshop on Lung Cancer of the American Cancer Society at Arden House in New York, February, 1959. This work is carried through in cooperation with his son, Felix D. Bertalanffy, Assistant Professor of Histology, University of Manitoba, Canada. Dr. von Bertalanffy is a Sloan Visiting Professor of the Menninger Foundation in Topeka, Kansas, U.S.A. He is currently publishing "Principles and Theories of Growth" as part of the monograph edited by W.W. Nowinski "Malignant Growth."

WERNER BICKENBACH OF MUNICH, GERMANY, is an honorary member of the Gynecological Society of Turkey. He is co-author (with G. Döring) of "Sterilität und Infertilität," published in June, 1959.

JORGE CAMPOS R. de C. OF LIMA, PERU, presented "The Relation between Histological Types of Cervical Carcinoma and Radio-Response" and "Histological Pattern of Carcinoma of the Cervix Associated with Pregnancy" at the first Peruvian Gynecological Congress in Lima, March 16 - 20. Dr. Campos is the General Secretary of the Conference. He wishes to announce that the First Peruvian National Cancer Conf. was held in Lima, June 25-27.

GIUSEPPE ERNESTO DELLEPIANE OF TURIN, ITALY, attended a conference on Karyology at the Broca Hospital in Paris in January, 1959. He will attend the Third World Congress of Sterility in Amsterdam. He became President of the European Society of Clinical Cytology and became an honorary member of the Austrian Society of Obstetrics and Gynecology. He recently participated in formulating the Constitution of the European Society of Clinical Cytology.

CLARICE DO AMARAL FERREIRA OF RIO DE JANEIRO, BRAZIL, will attend the Third World Congress of Fertility and Sterility at Amsterdam and the VII Congress Hispano-Luse de Obstetricia y Ginecologia in Spain. She recently became a Fellow of the American College of Surgeons. She recently published "Frigidez Sexual Feminia" and gave a course in Cytology in the Early Diagnosis of Cancer in the Colegio Brasileriro de Cirurgoces, in April, 1959.

ALVAN GLENN FORAKER OF JACKSONVILLE, FLORIDA, U.S.A., attended the Histochemical Society, the American Association of Cancer Research and the American Society of Experimental Pathology in Atlantic City. He also attended the International Academy of Pathology and the American Association of Pathologists and Bacteriologists in Boston and the Florida Medical Association in Miami this spring. He presented "pH Signature in Adenocarcinoma of the Colon" before the Histochemical Society and "The Interferometric Determination of Elastic Tissue Mass in Aortas of Adults and Infants" at the American Association of Pathology and Bacteriology and "The Cellular Basis of Otolaryngologic Practice" at the Florida Medical Association. He participated on the Committee for Research in Non-University Hospitals at the College of American Pathologists and on the Membership Committee of the International Academy of Pathology. He made the film, "Medical Research in a Community Hospital."

RUTH MOORE GRAHAM OF BUFFALO, NEW YORK, U.S.A., presented "Radiation Sensitivity and Radiation Response in Regard to Cytology" at the meeting of the Obstetrical and Gynecological Section of the Rochester Academy of Medicine on March 10. March 18 - 19, 1959, she instructed 65 pathologists in a postgraduate physicians course in cytology at Johns Hopkins Hospital in Baltimore, Maryland. During this session, she gave the following speeches, "Recurrent Carcinoma of the Cervix and its Diagnostic Problems," "Host-response," and "Sensitization Response and Radiation Response." Dr. Graham attended the Baton Rouge Obstetrical and Gynecological Society and the Sixth District Medical Societies on March 20 - 27, 1959, at which time she presented "Detection of Early Cervical Cancer and the Significance of the Atypical Smear" and "Studies on Optimum Treatment in Cancer of the Cervix." She attended the James Ewing Society Meeting in New York City, April 3, 1959, and presented "Cytologic Prognosis in Cancer of the Cervix."

J. EDWARD HALL OF BROOKLYN, NEW YORK, U.S.A., will give "The Significance of the Type III Smear" at the meeting of the American Association in September, 1959. He recently gave a course in Obstetrical and Gynecological Pathology at the State University of New York, Downstate Medical Center.

JOHN RODERICK HELLER OF WASHINGTON, D. C., U.S.A., attended the International Cancer Congress in London and the First National Cancer Congress in Lima, Peru, June 26 - 29, 1959.

JAN HEROLD OF PRAGUE, CZECHOSLOVAKIA, presented "Pre-cancer of the Uterine Cervix in Cytological Smears" on April 3 and 22 in Prague.

B. CORNELIS HOPMAN OF MIAMI, FLORIDA, U.S.A., gave a paper "A Clearing Technic in Endometrial Cytology" at the Sixth Annual Meeting in New York of the Inter-Society Cytology Council, November 15, 1958. He also presented a paper "Research in Cytology" at the Medical Faculty Research Seminar at Coral Gables, Miami, Florida, U.S.A., January 30, 1959.

WARREN C. HUNTER OF PORTLAND, OREGON, U.S.A., took part in the Cytology Committee at the College of American Pathologists and acted as Chairman, Ad Hoc Cytology Committee of the American Cancer Society.

IRENA KOPROWSKA OF PHILADELPHIA, PENNSYLVANIA, U.S.A., conducted a Symposium on Cytology at the Hahnemann Medical College, Philadelphia, Pennsylvania, on February 27, 1959. The Symposium marked the opening of the new Laboratory of Cytology. Dr. Koprowska spoke on "Induced Cervical Carcinoma as a Research Tool in Exfoliative Cytology." She also participated in the Meeting of the Inter-Society Cytology Council, she was the guest speaker at the Meeting of the Southeastern Chapter of the Pennsylvania Society of Medical Technologists, in April, 1959, and has been appointed Cytological Consultant to the New Jersey Society of Clinical Pathologists.

WARREN R. LANG OF PHILADELPHIA, PENNSYLVANIA, U.S.A., acted as Chairman of the Organizing Committee of the New York Academy of Sciences Conference on "The Vagina" April 10 - 11, 1959.

CAMILLE JEAN PIERRE LICHTFUS OF ARLON, BELGIUM, attended the Colloque de Cytologie de Paris where he gave "Vaginal Cytology at the End of Pregnancy" in May, 1959. He was recently made Chef de Clinique Adjoint a la Faculte de Medecine de STRASBOURG and is a member de l'Association Professionnelle des Obstetriciens et Gynecologues Belges.

NILO PEREIRA LUZ OF PORTO ALEGRE, BRAZIL, will spend six months at the Department of Obstetrics and Gynecology, University of Chicago, beginning July 1, 1959. On March 13, he participated in a round table discussion of "Habitual Abortion.

JOSEPH H. F. MAISIN OF LOUVAIN, BELGIUM, presented a paper on "Les Essais Therapeutique en Clinique" at the Conference organized by the Council for International Organizations of Medical Sciences in Vienna, Austria (March 23 - 27, 1959). He participated in the Annual Meeting of the International Committee on Laboratory Animals under the auspices of UNESCO in London, England, (April 11 - 13, 1959) and in the Sixth Session of the International Consultative Committee on Research in the Exact and Natural Sciences of UNESCO in Giessen, Germany, (April 20 - 24, 1959). Prof. Maisin attended the Symposium on the Immediate and Low Effect of Ionizing Radiation in Venice, Italy (June 22 - 26, 1959). He particpated in the Ninth International Congress on Radiology in Munich, Germany, and in the Meeting of "Shortening of Life Span of Mammals Following Irradiation" in London, England, July 6, 1959. Professor Maisin is active in the following committees at this time: Executive Committee of CIOMS, International Committee on Laboratory Animals, Editorial Committee of International Union Against Cancer, and Comité d'Experts de l'UNESCO and Committee on Cell Biology of UNESCO.

COLETTE MARSAN OF PARIS, FRANCE (Service du Prof. A. Sicard) became the Chief of Laboratories of the Medical Faculty of Paris and Attachee de Laboratoire a l'Hospital Beaujon. Dr. Marsan has been awarded the Sicard Award of the Medical Faculty of Paris.

KAZUMASA MASUBUCHI OF TOKYO, JAPAN, gave a lecture on "Early Diagnosis of Cancer of the Cervix" at the general meeting of the Japanese Medical Association on April 2 in Tokyo. He helped to establish the Japanese Cancer Society last year, acting as counselor and as a member of the Planning Committee.

SUBODH MITRA OF CALCUTTA, INDIA, visited the United States under the sponsorship of the Rockefeller Foundation. He was awarded the Berkeley Medal by the Asiatic Society. Dr. Mitra currently published a monograph entitled "Mitra Operation for Cancer of the Cervix," and he has finished a film on the same subject, which will be distributed by the American College of Surgeons.

JUNJI MIZUNO OF NAGOYA, JAPAN, participated in the Second World Gynecology Congress in Montreal, Canada and in the Thirty-second German Gynecology Congress in Frankfurt a. M., Germany. On his way around the world Dr. Mizuno visited cytology departments in various countries. He presented a paper on "The Present Status of Exfoliative Cytology in Western Countries" after his return to Japan before the Tokyo Obstetrical and Gynecological Society. Dr. Mizuno contributed the chapter, "Hormone Assay by Means of Exfoliative Cytology" to the monograph, "Clinical Examination in Obstetrics and Gynecology," published by Ishiyaku Shuppan of Tokyo.

GIUSEPPE MOGGIAN OF BOLOGNA, ITALY, recently published an Italian translation of "Klinische Fortschritte - Gynäkologie" by T. Antoine of Vienna, Austria.

LUIS MONTALVO-RUIZ OF MADRID, SPAIN, presented "Comments on the New Cytological Classification of the International Academy of Gynecological Cytologists" at the Sociedad Ginecologia Espanola in December, 1958. He also presented "Cytology of Amenorrhea" at a clinical session of la II Catedra of Obstetrics and Gynecology in Madrid in February, 1959.

ROBERT E. L. NESBITT, JR. OF ALBANY, NEW YORK, U.S.A., addressed the Rochester Academy of Medicine and the Montreal Obstetrical and Gynecological Society in February, 1959. He also spoke at the meeting of the Cleveland Obstetrical and Gynecological Society (March 6 - 8, 1959), at the American College of Obstetrics and Gynecology and at the Annual Meeting of the Medical Society of New Jersey (April, 1959). Dr. Nesbitt became the Chairman and Professor of Obstetrics and Gynecology of the Albany Medical College of Union University as of July 1, 1958.

GEORGE N. PAPANICOLAOU OF NEW YORK, NEW YORK, U.S.A., spoke at the opening of the new Cytology Laboratory of the Hahneman Medical College in Philadelphia, Pennsylvania, in February,

1959. Dr. Papanicolaou also gave a lecture in March, 1959, in a postgraduate physicians course in cytology at Johns Hopkins Hospital in Baltimore, Maryland. He recently became an Honorary Member of the Austrian Society of Gynecology and Obstetrics and received the Century Award from the General Federation of Women's Clubs.

HANNAH PETERS OF BOMBAY, INDIA, will be permanently situated in Copenhagen, Denmark. She is now working at the Finsen Laboratory, Finsen Institute and Radiumstation in Copenhagen, where she gave a paper on "Cell Changes Induced by Radiation in the Oral Cavity" in January, 1959.

WALTER SANDRITTER OF FRANKFURT am MAIN, GERMANY, gave a lecture on "Quantitative Methods in Histochemistry" at the Congress of Histochemistry in Warsaw, Poland. He recently wrote "UV-microspectrophotometry" in the Handbook of Histochemistry by G. Fischer. He recently made the film, "Color Interference Microcinematography on Hela-Cells in Tissue Culture (Mitosis)."

LEWIS CASS SCHEFFEY OF PHILADELPHIA, PENNSYLVANIA, U.S.A., gave a postgraduate teaching program at the Lovelace Foundation for Medical Education and Research in Alburquerque, New Mexico, January 27 - February 10, 1959. He is President of the American Gynecological Society and presented a speech at their meeting at Hot Springs, Virginia, May 21-23, 1959. He also received a citation from the Lovelace Foundation for Medical Education and Research in February, 1959.

EDMUND SCHÜLLER OF VIENNA, AUSTRIA, presented "Carcinoma Colli Uteri In Situ" at the London Ciba Symposium, May 8, 1959. He recently became an affiliate Member of Royal Society of Medicine. He also recently completed a film, "Ciliated Epithelia in the Endocervix."

HORST SMOLKA OF KIEL, GERMANY, has been elected a foreign correspondin,, member by the Société Royale Belge de Gynécologie et d'Obstétrique.

GUILLERMO TERZANO OF BUENOS AIRES, ARGENTINA, was appointed Head of the Department of Exfoliative Cytology at the Hospital of the University of Buenos Aires.

PREM NATH WAHI OF AGRA, INDIA, will present a paper at the Second World Conference on Medical Education in Chicago in August, 1959. He recently was elected a Fellow of the National Institute of Sciences of India. He was also awarded a grant by the National Institute of Health, Bethesda, Maryland, for the study of genital carcinoma in the women of Uttar Pradesh and was awarded a research grant by the State Research Council for a comparative cytological and histological study of experimentally produced carcinoma of cervix in mice.

GEORGE L. WIED OF CHICAGO, ILLINOIS, U.S.A., participated in a panel discussion on "Cervical Carcinoma, a Preventable Disease" at the Chicago Gynecological Society in February, 1959. March 18 - 21, he participated in the Postgraduate Institutes of Clinical Cytology at John Hopkins University in Baltimore, Maryland, where he presented "Cervical Visualization Techniques." Dr. Wied attended the New York Academy of Sciences, where he took part in the symposium "The Vagina" and presented "Antagonism and Synergism of Sex Steroids on the Vaginal Epithelium." He was also guest speaker at the First New Zealand Cancer Conference from April 20 - 24, where he presented "Pulmonary Cytology," "Cytology in Obstetrics and Gynecology," "Cytology for the General Practioner," and "Cytology of Fluids." Dr. Wied gave a course for pathologists and cytotechnicians in the Royal Women's Hospital, Melbourne, Australia from April 26 - May 22. June 6 - 12, he participated in the Third International Congress on Sterility and Fertility in Amsterdam, Holland and will present, together with Dr. M. Edward Davis, a paper on "Cytology After Steroid Hormone Administration in Prognosis of Pregnancy" and will be a member of a panel on diagnostic techniques.

ANNOUNCEMENTS

INTER-SOCIETY CYTOLOGY COUNCIL, will have its annual scientific meeting at the Statler Hilton Hotel in Detroit, Michigan, U.S.A., November 19, 20, 21, 1959. For details concerning the meeting write to Dr. Paul A. Younge, Secretary, 1101 Beacon Street, Brookline 46, Massachusetts, U.S.A.

WANTED OR AVAILABLE

It is the purpose of this column to promote international exchange of cytologists and cytotechnicians, to inform them of open permanent positions, and to inform employers of available cytology personnel. Persons interested in obtaining permanent positions as cytologists or cytotechnicians or in obtaining temporary fellowships in cytology (teaching, exchange, or training fellowships), and individuals or institutions offering such positions or openings are invited to write giving full information to: ACTA CYTOLOGICA, 5841 Maryland Avenue, Chicago 37, Illinois, U.S.A. Information supplied will be held strictly confidential.

While information received is subject to editing so that it conforms to the style of ACTA CYTOLOGICA, ACTA CYTOLOGICA cannot and do not assume responsibility for statements made by contributors.

OFFRES ET DEMANDES

Cette rubrique est destinée à favoriser l'échange international de cytologistes et de techniciens en cytologie. Elle renseignera sur les places permanentes vacantes et informera également sur le personnel cytologique disponible. Les personnes désirant obtenir une place permanente de cytologiste ou cytotechnicien, ou faire un stage temporaire en cytologie (enseignement, échange, training), et les instituts ou personnes offrant de telles places sont invités à écrire aux ACTA CYTOLOGICA (5841, Maryland Avenue, Chicago 37, Illinois, U.S.A.) en donnant tous les détails. Les informations reçues auront un caractère strictement confidentiel.

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STELLENANGEBOTE UND STELLENGESUCHE

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CYTOLOGISTS AND CYTOTECHNICIANS WANTED

CYTOLOGIST IN CHARGE WANTED for University Department of Obstetrics and Gynecology. Candidates must be Doctor of Medicine interested in teaching, research and special studies in Exfoliative Cytology. Foreign candidates must have mastered the English language and be acceptable to the local Medical State Board. The appointment would be initiated with the rank of of instructor with an annual salary of $7200.00, subject to merit increases in salary and promotion in rank. Candidates are requested to submit their curriculum vitae with bibliography (including available reprints of publications) and three references (out of whom at least one must be from the United States) to Russel R. de Alvarez, M. D., Professor and Executive Officer, Department of Obstetrics and Gynecology, University of Washington, Seattle 5, Washington, U.S.A.

MEDICAL RESEARCH TECHNOLOGIST WANTED trained or willing to be trained as a cytotechnician for work in the Department of Obstetrics and Gynecology at L.S.U. School of Medicine; Louisiana State Civil Service Employee; starting salary $3500.

QUALIFIED CYTOTECHNICIAN WANTED full-time for Department of Pathology of Medical College of Georgia, Augusta. Opportunities for research and teaching in medical school environment. New laboratories, well-equipped and air-conditioned. Attractive salary.

Apply: Dr. L. D. Stoddard, Professor of Pathology, Medical College of Georgia, Augusta, Georgia, U.S.A.

RESEARCH FELLOW IN GYNECOLOGICAL PATHOLOGY WANTED. The Baptist Memorial Hospital, Jacksonville, Florida, will offer a Research Fellowship in the general area of research in gynecologic pathology to begin in the summer of 1959. The hospital currently operates 272 beds. It was opened in September, 1955, in a new air-conditioned building directly on the St. Johns River. The laboratories are attractively located on the second floor with separate laboratories for Histology, Bacteriology, Hematology, Clinical Microscopy and Chemistry. A new research laboratory with animal facilities is located on the sixth floor. The hospital is approved for residency training in Pathologic Anatomy and Clinical Pathology. Requirements: Graduation from an approved medical school, one year of approved internship, and at least one year of approved residency training in pathology or in obstetrics-gynecology. Stipend: A stipend of $3800 per year with an additional $350 per year for one to two dependents. No maintenance is furnished. Uniforms are not furnished but are laundered without charge.

Applications and inquiries should be addressed to: Alvan G. Foraker, M.D., Pathologist, Baptist Memorial Hospital, 800 Miami Road, Jacksonville 7, Florida, U.S.A.

RESIDENCY FOR FOREIGN GRADUATE (Other than French) in Obstetrics and Gynecology offered in the Maternité de l'Hopital de Creteil, Paris, France. The applicant should have experience in surgical obstetrics and gynecology (caesarean sections, forceps, hysterectomy) prior to application. The applicant will receive training in general obstetrics and gynecology and will have the opportunity of working in the laboratories, especially in the cytology laboratory of Professor Jean de Brux. The opening for this position will be either November, 1959, or April, 1960, and is for the period of one year. The monthly salary is 45.000 to 50.000 French francs. For further details write to Docteur A. J. Bret, Chef de Service de la Maternite de l'Hopital de Creteil, 53 Avenue de Saxe, Paris 7, France.

CYTOTECHNOLOGIST OR REGISTERED MEDICAL TECHNOLOGIST WANTED. 250-bed general hospital in a college community of approximately 4,000 people wants cytotechnologist or registered medical technologist for its laboratory. 40-hour working week with occasional weekend duty. Residence for technicians available. Two weeks annual vacation, plus two weeks sick leave. Salary for this position is open. Any interested persons should write to: Dr. Elizabeth French. Director, Clinical Diagnostic Laboratories, Mary Hitchcock Memorial Hospital, 2 Maynard Street, Hanover, New Hampshire, USA.

CYTOLOGIST (EXFOLIATIVE) NEEDED as chief screener and supervisor of growing cytology laboratory. Approved ASCP school of cytotechnology. New modern laboratory in one of the largest private hospitals and research centers in the Midwest. Outstanding employee benefits. Salary $5000-6000, depending upon qualifications. Write to: Dr. Otto Saphir, Pathology Department, Michael Reese Hospital, Chicago 16, Illinois, USA.

CYTOLOGISTS AND CYTOTECHNICIANS AVAILABLE

CYTOLOGICALLY TRAINED RESIDENT, Male, citizen of West Germany.

Cytology Training:	Trained for one year in a teaching laboratory in the United States (approved by the American Board of Pathology for training Pathologists) and has finished a complete internship in the United States.
Wanted:	Appointment in a University Hospital in Germany or in the United States of America. Available as of January 1, 1960.
Code No.:	MD-1-1959, in care of the ACTA CYTOLOGICA, 5841 Maryland Avenue, Chicago 37, Illinois, U.S.A.

CYTOLOGIST-GYNECOLOGIST, Female, Age: 34, citizen of West Germany, single, graduate of West German Medical School (M.D. - Dr. Med.)

Medical Training:	Eligible for German Board of Obstetrics and Gynecology (Facharzt fuer Frauenheilkunde). Completed additional internship and full residency training in Obstetrics and Gynecology in the United States of America.
Cytology Training:	(1) in West German Medical School, Department of Obstetrics and Gynecology and (2) one and a half years full time Cytology Fellowship in a training center in the United States (approved by the American Cancer Society)
Wanted:	Position as a gynecologist in charge of Cytology Laboratory (with clinical work if desirable) in The United States of America, Canada or West-Berlin, Germany.
Code No.:	OMD 1/1/57, in care of ACTA CYTOLOGICA, 5841 Maryland Avenue, Chicago 37, Illinois, U.S.A.

CYTOLOGIST-PATHOLOGIST, Male, Age: 36, single, graduate from Italian University (M.D.), citizen of Italy.

Medical Training:	Pathologist with six years experience after completion of residency.
Cytology Training:	Self-trained.
Wanted:	Training Fellowship in Cytology or Research Associate in Cytology in Austria, Germany or Switzerland for 6 to 12 months.
Code No.:	LLM 1/1/57, in care of the ACTA CYTOLOGICA, 5841 Maryland Avenue, Chicago 37, Illinois, U.S.A.

GYNECOLOGIST, Male, Age: 33, citizen of Denmark, married, graduate of Danish University (M.D.)

Medical Training:	Completed internship and residency in Obstetrics and Gynecology, and 3-1/4 years staff member in University Hospital.
Cytology Training:	None
Wanted:	Training Fellowship in Cytology in Great Britain or Central Europe.
Code No.:	ANV 1/1/57, in care of the ACTA CYTOLOGICA, 5841 Maryland Avenue, Chicago 37, Illinois, U.S.A.

CYTOTECHNICIAN, Female, Age: 32, citizen of West Germany, single, registered medical technician.

Cytology Experience:	Chief-Cytotechnician 7 years in cytology laboratory of a University Department of Obstetrics and Gynecology in Germany. Experience in cancer cytology, endocrinological cytology and hematology.
Wanted:	Exchange fellowship for a period of several months with a cytology center in the United States of America, Brazil or Argentina. Will return to present position upon completion of fellowship.
Code No.:	RU 1/1/57, in care of the ACTA CYTOLOGICA, 5841 Maryland Avenue, Chicago 37, Illinois, U.S.A.

MEDICAL TECHNOLOGIST, Female, citizen of the United States, single.

Cytology Training:	Extensive training in anatomy and histology of female genital tract, hormonal evaluations, atypical cytology and carcinomas of the female genital tract with additional practical experience in the handling and processing of cytological material.

Wanted:	European position as a gynecological cytotechnologist, beginning July 1.
Code No.:	GAG 3/1/59, in care of the ACTA CYTOLOGICA, 5841 Maryland Avenue, Chicago 37, Illinois, USA.

TRAINED CYTOTECHNOLOGIST AVAILABLE FOR SCREENING. Cytotechnologist with ten years of experience wants screening at home for pathologists and physicians. Will accept processed slides only. Charge per case. Code no.: MIDDLEWEST 3/1/59, in care of the ACTA CYTOLOGICA, 5841 Maryland Avenue, Chicago 37, Illinois, USA.

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